PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 205/09, A61K 31/395, C07D 405/12 // (C07D 405/12, 205:00, 317:00)

A1

(11) International Publication Number: WO 97/41098

(43) International Publication Date: 6 November 1997 (06.11.97)

(21) International Application Number: PCT/EP97/01898

(22) International Filing Date: 15 April 1997 (15.04.97)

(30) Priority Data:
9608646.7 26 April 1996 (26.04.96) EP
(34) Countries for which the regional or international application was filed: GB et al.
9623756.5 15 November 1996 (15.11.96) EP
(34) Countries for which the regional or international application was filed: GB et al.
9625121.0 3 December 1996 (03.12.96) EP
(34) Countries for which the regional or international application was filed: GB et al.

(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): LEACH, Colin, Andrew [GB/GB]; (GB). HICKEY, Deirdre, Mary, Bernadette [IE/GB]; (GB). IFE, Robert, John [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). DHANAK, Dashyant [GB/US]; SmithKline Beecham Pharmaceuticals, 1250 South Collegeville Road, P.O. Box 5089, Collegeville, PA 19426-0989 (US). THEOBALD, Colin [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

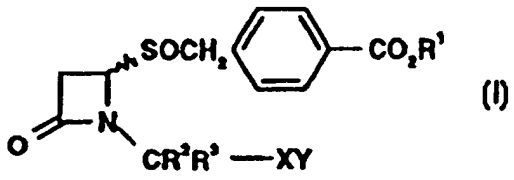
(74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AZETIDINONE DERIVATIVES FOR THE TREATMENT OF ATHEROSCLEROSIS

(57) Abstract



(I)

Selected compounds of formula (I) in which: R^1 is hydrogen or a corresponding pharmaceutically acceptable ester or a pharmaceutically acceptable salt thereof; R^2 and R^3 which may be the same or different is each selected from hydrogen or optionally substituted $C_{(1-6)}$alkyl; X is a group $X'(CH_2)_m$ in which X' is CO, $CONR^4$, COO, $CONR^4CO$, CONHO or CH_2O in which R^4 is hydrogen or $C_{(1-6)}$alkyl and m is 0 or an integer from 1 to 12; or a $C_{(1-12)}$alkylene chain optionally interrupted by X'; and Y is an optionally substituted aryl group; having the absolute configuration (*4R,5S*); are inhibitors of the enzyme Lp-PLA_2 and thereof of use in treating atherosclerosis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

AZETIDINONE DERIVATIVES FOR THE TREATMENT OF ATHEROSCLEROSIS

The present invention relates to certain novel monocyclic β-lactam compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A2 enzyme Lipoprotein Associated Phospholipase A_2 (Lp-PLA_2), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996:16;591-9) wherein it is referred to as LDL-PLA_2. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA_2 and suggest that it may have potential as a therapuetic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA_2 is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA_2 action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA_2 enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

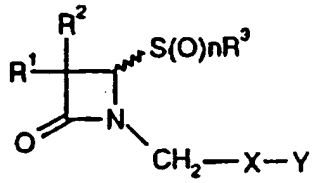
The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in

patients with atherosclerosis. Inhibitors of Lp-PLA_2 could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA_2 inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In addition, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA_2 activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

An earlier patent application (WO 96/19451, SmithKline Beecham plc) discloses compounds of the formula (A):



(A)

in which:

R^1 and R^2, which may be the same or different, is each selected from hydrogen, halogen or optionally substituted $C_{(1-8)}$alkyl;

R^3 is aryl or aryl$C_{(1-4)}$alkyl which may be optionally substituted;

X is a linker group;

Y is an optionally substituted aryl group; and

n is 0, 1 or 2.

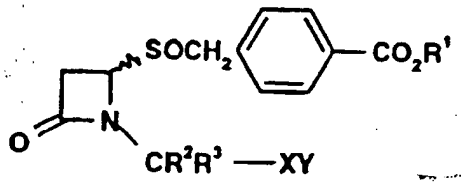
Such compounds of formula (A) are inhibitors of Lp-PLA_2 and as such are expected to be of use in treating atherosclerosis and the other disease conditions noted above.

WO 97/02242 (SmithKline Beecham plc) describes further compounds having a substiuent such a methyl on the carbon attached to N-1. In addtion,

PCT/EP96/05587 (SmithKline Beecham plc) discloses pro-drugs of compounds of formula (A) in which R^3 is a 4-carboxybenzyl group.

Compounds of formula (A) exist in a number of stereoisomeric forms. The C-4 carbon of the β-lactam ring is a chiral centre which will give rise to the presence of stereoisomers. Furthermore, in compounds of formula (A) in which n is 1, that is sulphoxide compounds, the presence of the SO moiety will introduce an additional chiral centre into the molecule and therefore give rise to the existence of extra stereoisomers. Preferred compounds of formula (A) are said to be those in which the relative configurations at C-4 and the SO moiety are *R,S* (*4R,SS*) and *S,R* (*4S,SR*) with the most preferred compounds having the absolute configuration (*4R,SS*).

Accordingly, the present invention provides for a compound of the formula (I):



(I)

in which:

R^1 is hydrogen or a corresponding pharmaceutically acceptable ester or a pharmaceutically acceptable salt thereof;

R^2 and R^3 which may be the same or different is each selected from hydrogen or optionally substituted $C_{(1-6)}$alkyl;

X is a group $X'(CH_2)_m$ in which X' is CO, $CONR^4$, COO, $CONR^4CO$, CONHO or CH_2O in which R^4 is hydrogen or $C_{(1-6)}$alkyl and m is 0 or an integer from 1 to 12, or a $C_{(1-12)}$alkylene chain optionally interupted by X'; and

Y is an optionally substituted aryl group;

having the absolute configuration (*4R,SS*).

Representative examples of X include $CO(CH_2)_m$, $CONH(CH_2)_m$, $COO(CH_2)_m$, $CONHCO(CH_2)_m$, $CONHO(CH_2)_m$ $CH_2O(CH_2)_m$ and $C_{(1-12)}$alkylene. Preferably, X' is CO, $CONR^2$ or CH_2O, more preferably CONH. Preferably, m is 1, 2, 5, 6, 7 or 9, preferably 6. Suitably, X is $CONH(CH_2)_6$ or $CH_2O(CH_2)_6$, preferably $CONH(CH_2)_6$.

Suitably, R^2 and R^3 is each hydrogen or R^2 is hydrogen and R^3 is methyl. Preferably, R^2 and R^3 is each hydrogen. It will be readily appreciated that when

R^2 and R^3 have different values, the carbon to which they are attached will be chiral. Preferably, the absolute configuration at this carbon is *S*. In such compounds of formula (I), the absolute configuration of the preferred enantiomer is (α-*S*, 4-*R*, S-*S*).

Suitably, Y is phenyl, optionally substituted by up to three further substituents. Suitable substituents include halo, hydroxy, $C_{(1-8)}$alkyl and $C_{(1-8)}$alkoxy. Preferably, Y is phenyl optionally substituted by halo, more preferably 4-chloro or 4-fluoro-phenyl, most preferably, 4-fluoro-phenyl.

Suitably X-Y is $CONH(CH_2)_6Ph(4\text{-}F)/(4\text{-}Cl)$.

Suitable pharmaceutically acceptable esters include $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl esters, as well as pharmaceutically acceptable *in vivo* hydrolysable esters. The skilled person will appreciate that simple $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl benzoate esters show little if any tendency to break down in the human body, to leave the parent acid or its salt, even though they may be susceptible to *in vivo* hydrolysis in animals such as rabbits and dogs. The term "*in vivo* hydrolysable ester" is not therefore conventionally considered to include such esters.

Suitable $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl esters include ethyl and allyl esters.

Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups for incorporation in R^1 include those which break down readily in the human body to leave the parent acid or its salt.

Suitable values of R^1 for use *in vivo* hydrolysable esters include:

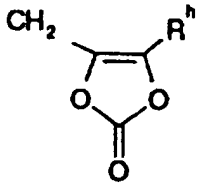
$-CH(R^a)O.CO.R^b$;

$-CH(R^a)O.CO.OR^c$;

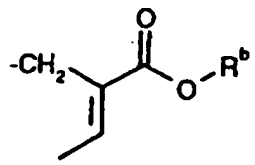
$-CH(R^a)CO.NR^eR^f$

$-R^dNR^eR^f$;

$-CH_2OR^g$;



$-CH(R^a)O.CO.C_6H_4Y^1COCH(R^i)NH_2$; and



in which:

R^a is hydrogen, $(C_1\text{-}6)$alkyl, in particular methyl, $(C_3\text{-}7)$cycloalkyl, or phenyl, each of which may be optionally substituted;

R^b is $(C_1\text{-}6)$alkyl, $(C_1\text{-}6)$alkoxy$(C_1\text{-}6)$alkyl, phenyl, benzyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl, 1-amino$(C_1\text{-}6)$alkyl, or 1-(C_1-6alkyl)amino$(C_1\text{-}6)$alkyl, each of which may be optionally substituted; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^c is $(C_1\text{-}6)$alkyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl;

R^d is $(C_1\text{-}6)$alkylene optionally substituted with a methyl or ethyl group;

R^e and R^f which may be the same or different is each $(C_1\text{-}6)$alkyl; or aryl$(C_1\text{-}4)$ alkyl, optionally substituted with e.g. hydroxy;

R^g is $(C_1\text{-}6)$alkyl;

R^h is hydrogen, $(C_1\text{-}6)$alkyl or phenyl;

R^i is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, $(C_1\text{-}6)$-alkyl, or $(C_1\text{-}6)$alkoxy;

and

Y^1 is oxygen or NH.

Suitable values of R^1 include:

(a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl, (1-aminoethyl)carbonyloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl and 4-methoxyphenyl-carbonyloxymethyl;

(b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl;

(c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;

(d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;

(e) lactone groups such as phthalidyl and dimethoxyphthalidyl;

(f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; and

(g) (2-methoxycarbonyl-*E*-but-2-en-yl)methyl.

Representative examples of R^1 include:
(2-methoxycarbonyl-*E*-but-2-en-yl)methyl, isobutyryloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl, 4-methoxyphenyl-carbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxy-carbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl, N,N-dimethylaminocarbonylmethyl, N-N-di-(2-hydroxyethyl)aminocarbonylmethyloxy and (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.

Especially preferred compounds of Formula (I) include:
(4*R*, *SS*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide and pharmaceuticaly acceptable salts thereof, in particular the sodium salt.

Since the compounds of Formula (I) are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of Formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of Formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation

conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of Formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A_2 (Lp-PLA_2) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of Formula (I) for use in therapy.

The compounds of Formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA_2 and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of Formula (I) may have a general application in any disorder that involves lipid peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid peroxidation in conjunction with Lp-PLA_2 activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with anti-hyperlipidaemic or anti-atherosclerotic or anti-diabetic or anti-anginal or anti-inflammatory or anti-hypertension agents. Examples of the above include cholesterol synthesis

inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository.

The compounds of Formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of Formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of Formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

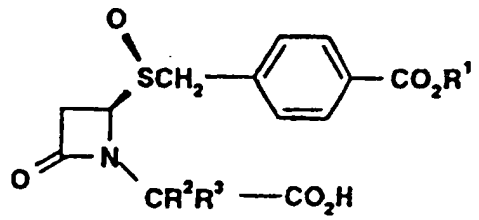
Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the Formula (I).

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the Formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Compounds of formula (I) may be prepared from convenient starting materials by adapting synthetic procedures well known in the art, with reference to earlier applications WO 96/19451 and WO 97/02242 (SmithKline Beecham plc).

Preferred compounds of formula (I) in which X is an amide CONH may be prepared by a process which comprises treating a compound of formula (II):



(II)

in which R^1 is $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl and R^2 and R^3 are as hereinbefore defined, and having the absolute configuration (4*R*,5*S*);
with an amine of the formula (III):

$$H_2N(CH_2)_nY$$

(III)

under suitable amide forming conditions, for instance in the presence of an activating agent such as N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in a suitable solvent such as dry dimethylformamide; and thereafter, and if necessary,

(a) removing the ester group under suitable de-esterifying conditions to form the acid;

(b) converting the acid to a pharmaceutically acceptable salt; and/or

(c) converting the acid, a suitable salt, the ester or an activated derivative of the acid, to an *in vivo* hydrolysable ester by reaction with a compound of formula (IV):

R^1R^4

(IV)

in which:

R^4 is a reactive esterifying leaving group; and

R^1 is as hereinbefore defined;

under ester forming conditions.

In step (a) above, the free acid may be regenerated from a corresponding compound in which the carboxy group is protected as a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl ester; using methods well known in the art for the particular protecting group, for instance, when an allyl group, using palladium catalysed de-allylation (triphenylphosphine/ pyrrolidine/ tetrakis triphenyl-phosphinepalladium(0) in dichloromethane).

In step (b) above, salts by prepared by treating the corresponding acid with an appropriate base.

Suitable ester forming conditions for use in step (c) above are well known in the art and are described in, for instance, Comprehensive Organic Synthesis, Pergamon Press, 1991, **6**, 323-380. Suitable ester forming conditions include:

(a) reacting a salt of the acid, for instance, a sodium or a tertiary amine salt such as triethylamine, with a compound of formula (IV), in a polar aprotic solvent such as dimethyl formamide, dimethyl sulphoxide or acetonitrile, at moderate temperature, for instance in the range 0 to 100°C;

(b) reacting the acid with a compound of formula (IV) in the presence of a base such as an alkali metal carbonate or a tertiary amine, in a polar aprotic solvent and temperature as for (a);

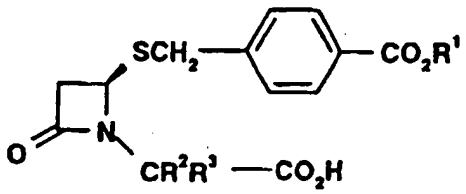
(c) reacting the acid with a compound of formula (IV) in which R^7 is a hydroxyl group, under dehydrating conditions, for instance the Mitsunobu reaction employing an azodicarboxylate and a trivalent phosphorus reagent (Mitsunobu, Synthesis, 1981, 1); or

(d) reacting an activated derivative of the acid, for instance a mixed anhydride, for instance an *iso*-butylcarbonic or a methane sulphonic anhydride or a carbodiimide (DCC) adduct, with a compound of formula (IV) in which R^7 is a hydroxyl group, in the presence of a suitable base such as a tertiaryamine, for instance, triethylamine, in an aprotic solvent such as tetrahydrofuran, at a moderate temperature, preferably in the range -20 to +20°C, or alternatively, in the absence of a base but using a preformed salt of the alcohol, for instance the magnesium or lithium alkoxide.

Preferred conditions include the use of the sodium salt of the acid in combination with a halide or sulphonate derivative of the compound of formula (IV).

Compounds of formula (II) are useful intermediates in the preparation of a compound of formula (I). Accordingly, in a further aspect, the present invention provides for a compound of formula (II) as hereinbefore defined.

Compounds of formula (II) are sulfoxides and may be readily prepared by oxidising a corresponding thio compound of formula (V):



(V)

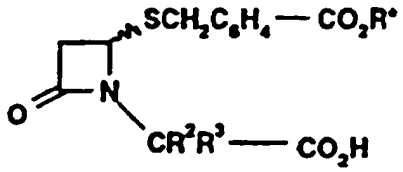
in which R^1, R^2 and R^3 are as hereinbefore defined, and having the absolute configuration (4*R*);
with a conventional oxidising agent such as m-chloroperbenzoic acid (mcpba) or ozone and thereafter and, if necessary, isolating the required diastereoisomer having the desired absolute configuration (4*R*, *SS*), for instance by fractional crystallisation and/or chromatography.

Compounds of formula (V) are of use in preparing compounds of formula (I). Accordingly, in a further aspect, the present invention provides for compounds of formula (V) as hereinbefore defined.

Compounds of formula (I) may also be obtained by an alternative process in which the two steps hereinbefore described are reversed, that is a compound of formula (V) is first treated with a compound of formula (III), to form the amide

bond, and the resultant thio intermediate then oxidised to the corresponding sulfoxide of formula (II), preferably using a chiral oxidising system which yields the required isomer as the predominant product.

Compounds of formula (V) having the absolute configuration (4*R*) may be obtained from the corresponding racemic compound of formula (VI):



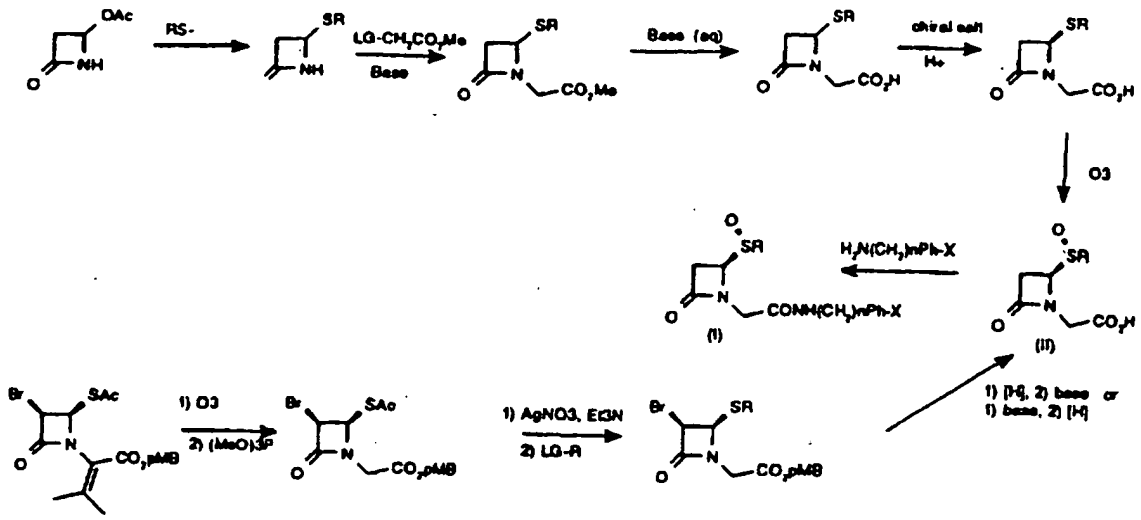
(VI)

in which R* is a carboxy protecting group, for instance $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl and R^2 and R^3 are as hereinbefore defined;
via the formation of a diastereoisomeric salt with a chiral base such as (-)-cinchonidine; and thereafter:
(a) isolating the preferred diastereoisomeric salt may be obtained by fractional crystallisation; and then
(b) generating the enantiomeric free acid therefrom by acidification.

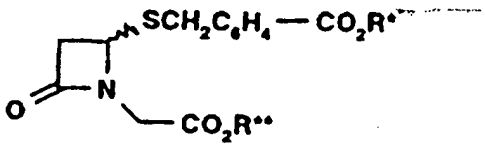
Diastereoisomeric salts formed from a compound of formula (VI) and a chiral base are of use in preparing compounds of formula (I). Therefore, in a further aspect, the present invention provides for such salts.

Compounds of formula (VI) may be obtained according to the procedures described in earlier applications WO 96/19451 and WO 97/02242 (SmithKline Beecham plc).

The process hereinbefore described for compounds of formula (I), as well as an alternative process for preparing compounds of formula (II), in which R^2 and R^3 is each hydrogen is summarised in the following scheme, in which R corresponds to $CH_2C_6H_4CO_2R^1$:



Compounds of formula (I) in which R^2 is hydrogen and R^3 is alkyl, for instance methyl, may be usefully prepared by a corresponding process in which the alkyl group is introduced at an early stage, by alkylating an azetidinone acetate of formula (VII):



(VII)

in which R** is $C_{(1-6)}$alkyl, for instance, methyl, and R* is as hereinbefore defined;

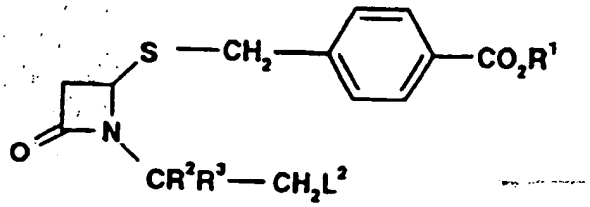
with an alkylating agent under standard alkylating conditions; and thereafter, isolating the diastereoisomers thus obtained by fractional crystallisation and/or chromatography. Suitably, the compound of formula (VII) may be a single enantiomer, having the required absolute configuration (4*R*).

Suitable alkylating agents include an alkyl iodide, in the presence of a suitable base such as sodium hydride or potassium hydroxide, optionally with a quaternary ammonium salt such tetrabutyl ammonium bromide, in a suitable alkylating solvent such as tetrahydrofuran (THF), and at a temperature in the range -10 to 0°C. Other suitable conditions include lithium bis(trimethylsilyl)amide in THF, optionally with 1,3-dimethylimidazolidin-2-one, and at a temperature of about -70°C.

The newly formed propionate ester may then be converted to the corresponding acid, using basic conditions such as aqueous sodium hydroxide in THF, followed by amide bond formation and then oxidation of the thio group, as previously described. Enantiomers may be usefully isolated by chiral chromatography, for instance hplc using a chiral stationary phase, on compounds of formula (I), at the alkyl/alkenyl ester stage.

The sequences can be readily adapted for other values of X, by reference to earlier applications WO 96/19451 and WO 97/02242 (SmithKline Beecham plc).

For instance, compounds of formula (I) in which the linker group X contains an ether function may be prepared by a suitable ether coupling reaction, for instance, when X' is CH_2O, treating a compound of formula (VIII):



(VIII)

in which R^1, R^2 and R^3 are as hereinbefore defined;
with a compound of formula (IX):

$$L^3(CH_2)_mY$$

(IX)

in which one of L^2 and L^3 is a halogen or another suitable leaving group such as triflate or tosylate and the other is OH or a suitable salt therof and m and Y are as hereinbefore defined; under standard ether forming conditions. The thus formed ether compound may then be treated with an oxidising agent to convert the thio group into a sulphinyl group, to give a compound of formula (I).

If the compound of formula (VIII) is a racemic compound, this will lead to a mixture of diastereoisomers. Oxidation of the thio group will create a further chiral centre and the resultant distereoisomers may be separated by fractional crystallisation and/or chromatography. Individual enatiomers may then be obtained by chiral chromatography.

Suitable compounds of formula (VIII) may be prepared by analogy with the processes described in WO 97/02242.

Compounds of formula (I) which are *in vivo* hydrolysable pharmaceutically acceptable esters may be conveniently prepared from the corresponding parent acid by a process which compromises treating the corresponding parent acid or a salt, alkyl ester or activated derivative thereof;

The present invention will now be illustrated by the following examples. Chiral compounds are described as 4*R* or 4*S*, *SR* or *SS* where the 4 describes the centre at the C4 position in the azetidinone and the S describes the sulfoxide centre. Diastereoisomer 1 derived from a 4*R* sulfide has the configuration 4*R*, *SR*. The corresponding diastereoisomer 2 is 4*R*, *SS*. Such configurations are by extropolation, based on their ^{1}H NMR spectra, from configurations obtained initially by x-ray analysis of a limited number of compounds. The absolute configuration at the chiral α-carbon, when one of R^2 and R^3 is hydrogen and the other is methyl, is described as α-*R* or α-*S*.

Example 1 - (R)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-all xycarbonylbenzylthio)-2-ox azetidin-1-yl)acetamide

a. Allyl 4-(br momethyl)benz ate

4-(Bromomethyl)benzoic acid (103 g, 0.48 moles)was suspended in thionyl chloride (200 ml) and dimethylformamide (1 ml) was added. The mixture was heated under reflux until clear, evaporated and azeotroped with toluene (2 x 150 ml). The resulting oil was dissolved in dichloromethane and added dropwise to a cooled solution of pyridine (42 ml) and allyl alcohol (40 ml) in dichloromethane. The mixture was stirred at room temperature for 1 hour, then washed with water, 2M hydrochloric acid, sodium hydrogen carbonate solution and brine. The organic solution was dried and evaporated to give allyl 4-(bromomethyl)benzoate as a clear oil (98g, 84% yield). ^{1}H NMR d ($CDCl_3$) 4.61 (2H, s, CH_2), 4.82 (2H, m, CH_2O), 5.34 (2H, m, CH_2CH-), 6.05 (1H, m, $CHCH_2$), 7.45 (2H, d, Ph-H), 8.03 (2H, d, Ph-H).

b. Allyl 4-(acetylthiomethyl)benzoate

Allyl 4-(bromomethyl)benzoate (98 g, 0.4 moles) in dry dimethylformamide (100 ml) was added dropwise to a cooled suspension of potassium thioacetate (46 g, 0.4 moles) in dry dimethylformamide (200 ml). The cooling bath was removed and the mixture was stirred overnight. The rection mixture was poured into water and extracted with ethyl acetate (x3). The combined extracts were washed with water and brine. The mixture was dried and evaporated to give allyl 4-(acetylthiomethyl)benzoate as an orange oil (100g, 100% yield). ^{1}H NMR d ($CDCl_3$) 2.36 (3H, s, $COCH_3$), 4.13 (2H, s, CH2), 4.82 (2H, m, CH_2O), 5.32 (2H, m, CH_2CH-), 6.05 (1H, m, $CHCH_2$), 7.35 (2H, d, Ph-H), 7.98 (2H, d, Ph-H).

c. 4-(4-(Allyloxycarbonyl)benzylthio)azetidin-2-one

Allyl alcohol (27 ml) in dry tetrahydrofuran (50 ml) was added dropwise to a solution of potassium *tert*-butoxide (4.93 g, 0.044 moles) in dry tetrahydrofuran (100 ml). After stirring for 5 minutes a solution of allyl 4-(acetylthiomethyl)benzoate (10.1 g, 0.04 moles) in dry tetrahydrofuran (100 ml) was added dropwise. After stirring for 15 minutes a solution of 4-acetoxyazetidin-2-one (5.16 g, 0.04 moles) was added dropwise. The mixture was stirred for 1 hour and evaporated. The residue was partitioned between ethyl acetate and water and the aqueouse was extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated. Flash chromatography (silica gel, ethyl acetate-petrol) gave 4-(4-allyloxycarbonylbenzylthio)azetidin-2-one as an oil (9.1g, 82% yield). ^{1}H NMR d ($CDCl_3$) 2.84 (1H, dd, H3a), 4.31 (1H, dd, H3b), 3.88 (2H, s, S-CH2), 4.68 (1H, dd, H4), 4.78 (2H, m, CH_2O), 5.35 (2H, m, CH_2CH-), 6.05 (1H, m, $CHCH_2$), 6.07 (1H, br. singlet, N-H), 7.40 (2H, d, Ph-H), 8.03 (2H, d, Ph-H).

d. Methyl 4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate

To a stirring solution of 4-(4-(allyloxycarbonyl)benzylthio)azetidin-2-one (2.55 g, 9.2 mmol), tetrabutylammonium bromide (0.33 g, 1.02 mmol) and methyl bromoacetate (1.06 ml, 11.2 mmol) in dry tetrahydrofuran (40 ml) was added powdered potassium hydroxide (0.63 g, 11.2 mmol) keeping the reaction temperature below 30 by means of a cold water bath. After 2 h, the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed (fine silica, ethyl acetate-petrol) to give the title compound as a clear oil, yield 2.66 g (83%).

^{1}H NMR δ ($CDCl_3$) 2.97 (1H, dd, H3a), 3.26, 4.07 (each 1H, CH_2CO, d), 3.42 (1H, dd, H3b), 3.70 (3H, s, CH_3O), 3.81 (2H, s, SCH_2), 4.83 (2H, m, CH_2O), 4.93 (1H, dd, H4), 5.35 (2H, m, CH_2CH), 6.03 (1H, m, $CHCH_2$), 7.39 (2H, d, Ph-H), 8.02 (2H, d, Ph-H)

e. (+/-)-4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid

To a solution of methyl 4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate (2.17 g, 6.21mmol) in tetrahydrofuran (20 ml) was added dropwise with cooling (ice bath) over 10 min a 1 molar aqueous solution of potassium hydroxide. After a further 30 min, the solution was diluted with water and extracted twice with ether. The aqueous layer was then acidified (dil. hydrochloric acid) with cooling and the oil which precipited was extracted into ether. The combined extracts were dried ($MgSO_4$) and evaporated to a clear oil which eventually crystallised under petrol and was filtered, washed and dried to give the title compound as white crystals, 1.87 g, 90% yield

^{1}H NMR δ ($CDCl_3$) 2.98 (1H, dd, H3a), 3.34, 4.06 (each 1H, CH_2CO, d), 3.42 (1H, dd, H3b), 3.82 (2H, s, SCH_2), 4.82 (2H, m, CH_2O), 4.92 (1H, dd, H4), 5.34 (2H, m, CH_2CH), 6.03 (1H, m, $CHCH_2$), 7.39 (2H, d, Ph-H), 8.02 (2H, d, Ph-H)

f. (-)-(R)-4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid

4-(4-(Allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid (3.41 g, 10.2 mmol) and cinchonidine (2.99 g, 10.2 mmol) in ethanol (40 ml) were heated to boiling when a clear solution was obtained. On standing for 90 min, the crystalline salt which had precipitated was filtered off, and recrystallised from ethanol (20 ml). The solid obtained was stirred vigorously with ether and water whilst acidifying with dil. hydrochloric acid, and when complete solution was obtained the layers were separated and the aqueous layer further extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oil which crystallised on trituration with light petrol to give the title compound as white crystals, m.p. 74-6°C, 6.7 g, 50% yield

a_D^{25} = -24.2 (c. 0.7 w/v $CHCl_3$, 25°C)

^{1}H NMR δ ($CDCl_3$) 2.97 (1H, dd, H3a), 3.26, 4.07 (each 1H, CH_2CO, d), 3.42 (1H, dd, H3b), 3.70 (3H, s, CH_3O), 3.81 (2H, s, SCH_2), 4.83 (2H, m, CH_2O),

4.93 (1H, dd, H4), 5.35 (2H, m, CH_2CH), 6.03 (1H, m, $CHCH_2$), 7.39 (2H, d, Ph-H), 8.02 (2H, d, Ph-H)

g. (R)-N-[6-(4-Fluor phenyl)hex-1-yl]-4-(4-alloxycarbonylbenzylthi)-2-xoazetidin-1-yl)acetamide

To a cooled (ice bath) solution of (R)-4-(4-(allyloxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid (12.51 g, 0.0373 mol), 1-hydroxybenzotriazole hydrate (5.04 g, 0.0373 mol) and 6-(4-fluorophenyl)hexylamine (0.0373 mol) in dry dimethylformamide (150 ml) was added with stirring dicyclohexylcarbodiimide (7.29 g, 0.0373 mol). After 20 min the cooling bath was removed, and after a further 16 h, the solvent was evaporated under reduced pressure and the residue treated with ethyl acetate and the insoluble precipitate filtered off and discarded. The filtrate was further diluted with ethyl acetate, washed with 0.2 M hydrochloric acid, then saturated sodium hydrogen carbonate, dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/light petrol to give the title compound as white crystals, m.p. 54-7°C, 17 g, 89% yield

^{1}H NMR δ ($CDCl_3$) 1.30-1.60 (8H, m, 4xCH_2), 2.55 (2H, t, J=7.6 Hz, CH_2Ph), 2.90, 2.97 (1H, dd, J=2.4, 15.4 Hz, H_3), 3.23 (2H, m, $NHCH_2$), 3.35, 3.41 (1H, dd, J=5.1, 15.4 Hz, H_3), 3.53, 3.78 (each 1H, d, J=16.6 Hz, NCH_2), 3.86 (2H, s, SCH_2), 4.83 (3H, m, CO_2CH_2, H_4), 5.37 (2H, m, CH_2=CH), 6.0 (2H, m, NH, CH_2=CH), 6.94 (2H, m, 4-FPh-H), 7.10 (2H, m, 4-FPh-H), 7.39 (2H, d, J=8.3 Hz, 4-CO_2allylPh-H), 8.02 (2H, d, J=8.3 Hz, 4-CO_2allylPh-H)

Example 2 - (4*R*, S*S*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-alloxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (R)-N-[6-(4-fluorophenyl)hex-1-yl]-4-(4-alloxycarbonylbenzylthio)-2-oxoazetidin-1-yl)acetamide (16.36 g, 0.0319 mol) in dichloromethane (150 ml) was cooled to -65 to -70 and a solution of *m*-chloroperbenzoic acid (6.61 g, 0.0383 mol) in dichloromethane (120 ml) added dropwise with stirring over 20 min. After 1 h, the mixture was washed with saturated sodium metabisulphite solution, then saturated sodium hydrogen carbonate, then dried ($MgSO_4$) and evaporated to a solid which was recrystallised from ethyl acetate to give a mixture of diastereoisomers 2 and 1 in the ratio 3:2. Chromatographic separation (HPLC) gave diastereomer 2 (4*R*, S*S*) as a white crystalline solid, m.p. 133-5°C, 3.3 g, 20% yield

$a_D^{25°C}$ = +74.0 (c. 0.6% w/v $CHCl_3$, 25°C)

^{1}H NMR δ ($CDCl_3$) 1.30-1.60 (8H, m, 4xCH_2), 2.56 (2H, t, J=7.6 Hz, CH_2Ph), 2.91, 2.95 (1H, dd, J=2.4, 15.2 Hz, H_3), 3.27 (3H, m, $NHCH_2$, H_3), 3.94, 4.22 (each 1H, d, J=17.2 Hz, NCH_2), 4.04, 4.18 (each 1H, d, J=12.8 Hz, $SOCH_2$), 4.65 (1H, m, H_4), 4.84 (2H, m, CO_2CH_2), 5.37 (2H, m, CH_2=CH), 6.0 (1H, m,

CH_2=CH), 6.95 (3H, m, 4-FPh-H, NH),), 7.10 (2H, m, 4-FPh-H), 7.36 (2H, m, 4-CO_2allylPh-H), 8.09 (2H, m, 4-CO_2allylPh-H).

Example 3 - (4*R*, S*R*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-all xycarbonylbenzylsulphinyl)-2- xoazetidin-1-yl)acetamide

From the HPLC chromatography described in Example 2 above the other diastereoisomer (Dia 1: 4*R*, S*R*) was obtained as a white crystalline solid (1.8 g, 11% yield) m.p. 175-7°C

$a_D^{25°C}$ = -119.7 (c. 0.5% w/v $CHCl_3$, 25°C)

^{1}H NMR δ ($CDCl_3$) 1.30-1.60 (8H, m, 4xCH_2), 2.55 (2H, t, J=7.6 Hz, CH_2Ph), 2.95, 2.98 (1H, dd, J=4.8, 14.8 Hz, H3), 3.24 (2H, m, $NHCH_2$), 3.42, 3.46 (1H, dd, J=2.4, 14.8 Hz, H3), 3.76, 4.09 (each 1H, d, J=17.2 Hz, NCH_2), 3.95, 4.01 (each 1H, d, J=13.2 Hz, $SOCH_2$), 4.59 (1H, m, H4), 4.84 (2H, m, CO_2CH_2), 5.37 (2H, m, CH_2=CH), 6.0 (1H, m, CH_2=CH), 6.53 (1H, m, NH), 6.95 (2H, m, 4-FPh-H), 7.10 (2H, m, 4-FPh-H), 7.36 (2H, d, J=8 Hz, 4-CO_2allylPh-H), 8.09 (2H, d, J=8 Hz, 4-CO_2allylPh-H).

Example 4 - (4*R*, S*S*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-alloxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (Example 2) (0.185 g, 0.35 mmol), triphenylphosphine (0.092 g, 0.35 mmol), pyrrolidine (0.033 ml, 0.4 mmol) and tetrakis triphenylphosphinepalladium(0) (0.012 g, 0.01 mmol) in dichloromethane (10 ml) was stirred under nitrogen for 16 h. A further 0.012 g (0.01 mmol) of tetrakis triphenylphosphinepalladium(0) was added and after a further 4 h the reaction was complete. The solution was diluted with water, acidified (2N HCl), the layers separated and the aqueous layer further extracted with dichloromethane. The combined extracts were dried ($MgSO_4$)and evaporated to a yellow oil, which was triturated with ether. A yellow solid was obtained which was filtered off and dissolved in sodium hydrogen carbonate solution. Shaking with ether gave an emulsion which was separated by treatment with ethyl acetate and centrifugation. The aqueous layer was then acidified (2N HCl) and extracted with dichloromethane, and the extracts dried ($MgSO_4$)and evaporated. The residue was triturated with ether to give a white solid which was filtered, washed and dried to give the title compound as a white solid, m.p. 105-7°C, 0.1 g, 58% yield

$a_D^{25°C}$ = -31.7 (c. 0.5% w/v DMSO, 25°C)

^{1}H NMR δ (DMSO) 1.26 (4H, m, 2xCH_2), 1.38 (2H, m, CH_2), 1.50 (2H, m, CH_2), 2.96, 2.99 (1H, dd, J=2, 15.2 Hz, H), 3.06 (2H, m, $NHCH_2$), 3.84, 4.09 (each 1H, d, J=17.2 Hz, NCH_2), 4.13, 4.31 (each 1H, d, J=12.8 Hz, $SOCH_2$), 4.84

(1H, m, H), 7.05 (2H, m, 4-FPh-H), 7.19 (2H, m, 4-FPh-H), 7.47 (2H, d, J=8 Hz, 4-CO_2allylPh-H), 7.93 (2H, d, J=8 Hz, 4-CO_2allylPh-H), 8.13 (1H, m, NH), 13 (1H, bs, CO_2H).

Example 5 - (-)-(4*R*, *SS*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamid , sodium salt

A mixture of N-[6-(4-fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.51 g) and sodium bicarbonate (0.088 g) in water (15 ml) was sonicated for 5 min, methanol added (20 ml) and the mixture sonicated for a further 20 min. After filtration the solution was evapotated to a low volume, diluted with water and lyophilised to give the title compound as a white powder (0.52 g), m.p. 238-40°C. a_D = -31.7° (c 0.5, DMSO)

Example 6 - 4*R*, *SS*-N-(6-(4-Fluorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide

a. Ethyl 4-(bromomethyl)benzoate

4-(Bromomethyl)benzoic acid (25.75g, 0.1197moles) was suspended in thionyl chloride (50ml) and dimethylformamide (0.25ml) was added. The mixture was heated under reflux for 25 minutes until clear, evaporated and azeotroped with toluene (x2). The resulting oil was dissolved in dichloromethane (75ml) and added dropwise over 10 minutes to a solution of absolute alcohol (8.6ml, 0.1465moles), pyridine (10.5ml, 0.1298moles) in dry dichloromethane (50ml), cooled to 10°C. The ice bath was removed and the reaction was stirred for 45 minutes , then washed with water, 2NHCl, water, sodium hydrogen carbonate solution and brine. The organic solution was dried ($MgSO_4$) and evaporated to give a mixture of 60:40 ethyl 4-(bromomethyl)benzoate: ethyl 4-(chloromethyl)benzoate as an oil (25.6g, 94%)

^{1}H nmr δ ($CDCl_3$) 1.40 (3H, m, CH_3), 4.40 (2H, m, CH_2O), 4.50, 4.61 (2H, 2xs, CH_2Cl/Br), 7.45 (2H, m, Ar-H), 8.01 (2H, m, Ar-H)

b. Ethyl 4-(acetylthiomethyl)benzoate

60:40 Ethyl 4-(bromomethyl)benzoate: ethyl 4-(chloromethyl)benzoate (25.0g, 0.111moles) in dry dimethylformamide (150ml), cooled to 5°C, was treated with potassium thioacetate (13.3g, 0.117moles) and the temperature rose to 20°C. The reaction was stirred at room temperature for 2 hours, poured into water (250ml) and extracted with diethyl ether (3x100ml). The organic extracts were combined, washed with water, dried ($MgSO_4$), charcoaled and evaporated to give ethyl 4-(acetylthiomethyl)benzoate as a brown soild (26.0g, 99%), m.p. 36-37°C.

^{1}H nmr δ ($CDCl_3$) 1.38 (3H, t, J=7.1Hz, CH_3), 2.36 (3H, s, $COCH_3$), 4.14 (2H, s, CH_2S), 4.36 (2H, q, CH_2O), 7.35 (2H, d, J = 8.2Hz, Ar-H), 7.97 (2H, d, J= 8.2Hz, Ar-H)

c. 4-(4-(Eth xycarbonyl)benzylthio)azetidin-2-one

A solution of sodium (1.87g, 0.0813moles) in absolute alcohol (300ml) was treated with a solution of ethyl 4-(acetylthiomethyl)benzoate (19.4g, 0.0814moles) in absolute alcohol (75ml) over 3 minutes. The reaction was stirred at room temperature for 30 minutes, cooled to -5°C and treated with a solution of 4-acetoxyazetidin-2-one (10.0g, 0.07745moles) over 5 minutes. The cooling bath was removed and reaction was stirred for 2 hours, evaporated to dryness and treated with brine (200ml) and extracted with ethyl acetate (200ml, 100ml). The organic extracts were combined washed with brine, dried ($MgSO_4$) and evaporated to a red oil. Purified by flash column chromatography on silica gel eluted with 3:1 to 1:2 petroleum ether 40-60°C:ethyl acetate to give 4-(4-(ethoxycarbonyl)benzylthio)azetidin-2-one as an orange oil (18.64g, 91%).
^1H nmr δ ($CDCl_3$) 1.38 (3H, t, J=7.1Hz, CH_3), 2.82, 2.89 (1H, 2xm, H_3), 3.29, 3.35 (1H, 2xm, H_3), 3.88 (2H, s, CH_2S), 4.37 (2H, q, CH_2O), 4.70 (1H, m, H_4), 5.70 (1H,bs, NH), 7.40 (2H, d, J = 8.3Hz, Ar-H), 8.00 (2H, m, Ar-H)

d. Methyl (4-(4-ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate

A stirred solution of 4-(4-(ethoxycarbonyl)benzylthio)azetidin-2-one (217.3g, 0.819mol), methyl bromoacetate (128.5g,0.84mol) and tetrabutylammonium bromide (25.8g,0.08mol) in dry THF (900ml) was cooled in an ice bath to 20°C and finely ground potassium hydroxide (48.3g, 0.86mol) was added in one portion. The reaction exothermed to 45°C and was allowed to cool back to 30°C when the ice bath was removed and stirring continued for 1hr. More potassium hydroxide (2.4g, 0.043mol) was added and stirred 30mins when this addition was repeated. After a further 30mins, the reaction mixture was filtered through hyflo, washing with more THF. The combined organics were evaporated to a red oil. Ether (1l) was added an shaken well. The ether was decanted and the process repeated. The combined ether extracts were evaporated to give the title compound as a dark red oil (199.8g, 72% yield)
^1H NMR δ ($CDCl_3$), 1.40 (3H, t, J=7Hz, CH_2CH_3), 2.98 (1H, dd, J=2, 15 Hz, H_3), 3.26, 4.03 (each 1H, d, J=18 Hz, NCH_2), 3.42 (1H, dd, J=5, 15 Hz, H_3), 3.70 (3H, s, OCH_3), 3.81, (2H, m, SCH_2), 4.38 (2H, q, J=7 Hz, OCH_2), 4.93 (1H, m, H_4), 7.39 (2H, m, Ph-H), 7.99 (2H, m, Ph-H).

e. (4-(4-Ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid

Methyl (4-(4-ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetate (169.8g,0.503mol) was disolved in THF (750ml), cooled to 0°C and a solution of potassium hydroxide (29.7g, 0.529mol) in water (500ml) was added over 15min at 0 - 5°C then the mixture was stirred at 0°C for 45mins. Ether (1l) and water (2l) were added, the layers separated and the aqueous washed with ether (1l), then acidified with conc hydrochloric acid (55ml) and extracted with dichloromethane

(2 x 1l). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the title compound as a green solid (128.4g, 79% yield).

f. (-)-R-(4-(4-Ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid

4-(4-Ethoxycarbonyl)benzylthio)-2-oxoazeyidin-1-ylacetic acid (46.0g, 0.1422moles) and (-)-cinchonidine (41.88g, 0.1423moles) were dissolved in abolute alcohol (450ml). The solution was cooled for 1.5 hours, filtered, and dried to give the salt as a cream solid (33.15g). This solid was recrystallised from absolute alcohol (300ml) to give 23.6g of salt which was mixed with water (500ml) and diethyl ether (500ml) and acidified with dilute HCl (50ml). When all the solid had dissolved the layers were separated and the aquous layer was extracted with ether (250ml). The organic extracts were combined, ethyl acetate (100ml) was added and washed with water, dried ($MgSO_4$), filtered and evaporated to give R-(4-(4-ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid as a colourless solid. (10.93g, 23.8%) m.p. 135-137°C.

a_D = -23.5 (c = 0.46 w/v in chloroform at 25°C)

^{1}H NMR δ ($CDCl_3$) 1.39 (3H, t, J=7.1Hz, CH_3), 2.96, 3.02 (1H, dd, J =2.2, 15.3 Hz, H3), 3.33, 4.05 (each 1H, d, J=18.4 Hz, NCH_2CO_2H), 3.40, 3.46 (1H, dd, J= 5.1, 15.3 Hz, H3), 3.82 (2H, s, SCH_2), 4.37 (2H, q, CO_2CH_2), 4.68 (1H, b, CO_2
H), 4.92 (1H, m, H4), 7.38 (2H, d, J=8.2Hz, Ph-H), 7.99 (2H, d, J=8.2Hz, Ph-H)

g. 4*R*,S*R*-(4-(4-Ethoxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-ylacetic acid (diastereoisomer 1)

h. 4*R*,S*S*-(4-(4-Ethoxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-ylacetic acid (diastereoisomer 2)

A solution of (-)-*R*-(4-(4-ethoxycarbonyl)benzylthio)-2-oxoazetidin-1-ylacetic acid (10.81g, 0.03343moles) in dry dichloromethane (400ml) at -70°C was treated with ozone until a blue colouration appeared. The reaction was allowed to warm to room temperature and dichloromethane (50ml) was added to aid stirring. The solution was evaporated to dryness and the resulting soild was mixed with chloroform (200ml). The colourless solid was collected by filtration to give 4*R*,S*R*-(4-(4-ethoxycarbonyl)benzylsulphinyl-2-oxoazetidin-1-ylacetic acid (4.11g, 36%) m.p.162-164°C. (contains 15.8:1 dia1:dia2)

^{1}H NMR δ (DMSO) 1.33 (3H, t, J=7Hz, CH_3), 2.97, 3.04 (1H, dd, J=4.8,14.8Hz, H3), 3.12, 3.16 (1H, dd, J= 1.6, 14.8Hz, H3), 3.83, 4.17 (each 1H, d, J= 18Hz, NCH_2CO_2H), 4.92, 4.24 (1H, d, J = 12.8Hz, $SOCH_2$), 4.32 (2H, q, CO_2CH_2), 4.99 (1H, m, H4), 7.48 (2H, d, J=8.0Hz, Ph-H), 7.96 (2H, d, J=8.0Hz, Ph-H)

The filtrate from the above was evaporated, mixed with diethyl ether and filtered to give 4*R*,S*S*-(4-(4-ethoxycarbonyl)benzylsulphinyl-2-oxoazetidin-1-ylacetic acid (6.42, 56%) m.p. 152-155°C. (contains 92:8 dia2:dia1)

^{1}H NMR δ (DMSO) 1.33 (3H, t, J=7 Hz, CH_3), 2.97, 3.01 (1H, dd, J=2.0,15.5Hz, H_3), 3.35 (1H, m, H_3), 3.95, 4.17 (each 1H, d, J= 18.2Hz, NCH_2CO_2H), 4.15 (1H, d, 1 of $SOCH_2$), 4.32 (3H, m, 1 of $SOCH_2$, CO_2CH_2), 4.82 (1H, m, H_4), 7.51 (2H, d, J=8.2Hz, Ph-H), 7.97 (2H, d, J=8.2Hz, Ph-H)

i. (+)-4*R*, *SS*-N-(6-(4-Fluorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide

6-(4-Fluorophenyl)hexylamine (1.82g, 0.00932moles) in dry dimethylformamide (75ml) was added to a mixture of 4*R*,*SS* -(4-(4-ethoxycarbonyl)benzylsulphinyl-2-oxoazetidin-1-ylacetic acid (3.15g, 0.00928moles), N,N,-dicyclohexylcarbodiimide (1.92g, 0.00931moles) and 1-hydroxybenzotriazole (1.25g, 0.00925moles). The reaction was stirred at room temperature for 3.5 hours, diluted with ethyl acetate (100ml) and cooled. The mixture was filtered to remove urea and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate (400ml), washed with sodium hydrogen carbonate solution, brine, dried and evaporated to a colourless solid (5.8g) which was recrystallised from ethyl acetate (125 ml) to give the product (3.0g). Purification by column chromatography gave 4*R*,*SS* -(4-(4-ethoxycarbonyl)benzylsulphinyl-2-oxoazetidin-1-ylacetic acid as a colourless solid, 155-156°C, 1.8 g, 38% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.6 (11H, m, 4xCH_2, CH_3), 2.56 (2H, t, J = 7.6Hz, CH_2Ph), 2.89, 2.96 (1H, dd, J=2.4,15.3Hz, H_3), 3.25 (3H, m, $NHCH_2$, H_3), 3.94, 4.22 (each 1H, d, J=17Hz, NCH_2CO), 4.03, 4.18 (each 1H, d, J=12Hz, $SOCH_2$), 4.39 (2H, q, CO2CH_2), 4.65 (1H, m, H_4), 6.9-7.12 (5H, m, NH,p-ClPh-H), 7.35 (2H, d, J=8.3Hz, Ph-H), 8.07 (2H, d, J=8.3Hz, Ph-H)

a_D = +85.2 (c = 0.5% w/v in chloroform at 25°C)

Found: C, 62.6; H, 6.3; N, 5.4%; $C_{27}H_{33}FN_2O_5S$ requires: C, 62.8; H, 6.4; N, 5.4%

Example 7 - (+)-4*R*, *SS*-N-(6-(4-Chlorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide

Treatment of 4*R*,*SS*-(4-(4-ethoxycarbonyl)benzylsulphinyl-2-oxoazetidin-1-ylacetic acid with 6-(4-chlorophenyl)hexylamine, N,N-dicyclohexylcarbodiimide, and 1-hydroxybenzotriazole in dry dimethylformamide as described for Example 6 above, followed by the same work-up procedure gave the title compound as a colourless solid, 159-161°C, 45% yield

^{1}H NMR δ ($CDCl_3$) 1.3-1.6 (11H, m, 4xCH_2, CH_3), 2.56 (2H, t, J = 7.6Hz, CH_2Ph), 2.89, 2.95 (1H, dd, J=2.4,15.3Hz, H_3), 3.25 (3H, m, $NHCH_2$, H_3), 3.94, 4.24 (each 1H, d, J=17Hz, NCH_2CO), 4.03, 4.18 (each 1H, d, J=12Hz, $SOCH_2$), 4.36 (2H, q, CO2CH_2), 4.65 (1H, m, H_4), 7.04 (1H, m, NH), 7.06-7.26 (4H, m, p-ClPh-H), 7.35 (2H, d, J=8.3Hz, Ph-H), 8.07 (2H, d, J=8.3Hz, Ph-H)

a_D = +83.9 (c = 1.0% w/v in chloroform at 25°C)
Found: C, 60.9; H, 6.1; N, 5.2%; $C_{27}H_{33}ClN_2O_5S$ requires: C, 60.8; H, 6.2; N, 5.3%

Example 8 - (+)-4*R*, S*S*-N-(6-(4-Fluorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide

a. *p*-Methoxybenzyl [(3*S*, 4*R*)-4-acetylthio-3-bromo-2-oxoazetidin-1-yl]acetate

Ozonised oxygen was bubbled through a solution of p-methoxybenzyl 2-[(3*S*, 4*R*)-4-acetylthio-3-bromo-2-oxoazetidin-1-yl]-3-methylbut-2-enoate (Osborne N. F. et al., J. Chem. Soc., Perkin Trans. 1, 1994, 179) (20.16 g, 0.0456 mol) in ethyl acetate (400 ml) at -65 to -70°C until a permanent blue solution was obtained. Excess ozone was removed by the passage of oxygen, then trimethyl phosphite (53.8 ml, 0.456 mol) was added dropwise. After 15 min. the solution was allowed to warm to room temperature, then stood for 16 hr. The solvents were evaporated and the residue reevaporated twice from toluene,then dissolved in ethyl acetate (300 ml) and stirred vigorously for 1.5 hr. with a solution of *p*-toluenesulphonic acid (2 g) in water (100 ml). After dilution with water the organic layer was separated and the aqueous layer further extracted with ethyl acetate. The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate and brine, then dried ($MgSO_4$) and evaporated. Purification by flash chromatography (silica, ethyl acetate-pet. ether) gave the title compound as a light brown oil, yield 10.6 g (58%).

b. Silver (3*S*,4*R*)-3-bromo-1-(*p*-methoxybenzyloxycarbonylmethyl)-2-oxoazetidine-4-thiolate

A solution of *p*-methoxybenzyl [(3*S*, 4*R*)-4-acetylthio-3-bromo-2-oxoazetidin-1-yl]acetate (4.13 g, 0.01 mol) in methanol (90 ml) was added with stirring in subdued light to a solution of silver nitrate (2.27 g, 0.0133 mol) in methanol (90 ml). Triethylamine (1.87 ml, 0.0133 mol) was then added with ice cooling, and stirring continued for 1 hr. at 5-10°C followed by 30 min. at room temperature. The mixture was re-cooled (ice bath) and the precipitated solid filtered and washed twice with ice cold methanol then hexane to give the title compound, yield 4.6 g (96%).

c. 4-Carbethoxybenzyl iodide

Treatment of 4-carboxybenzylbromide with thionyl chloride followed by ethanol in pyridine have a mixture of 4-carbethoxybenzyl chloride and bromide which was treated (14.6 g) with sodium iodide (39.8g) in acetone (150ml) at reflux temperature for 20hrs. The mixture was cooled, filtered and the solvent evaporated off. The residue was taken up in ether (150ml) and washed with

water, aqueous sodium thiosulphate, water, brine, dried and evaporated to give the title compound as a pale yellow solid, m.p. 61-3°C, 17.5 g (91% yield).
^{1}H NMR δ ($CDCl_3$) 1.39(3H, t, J=7.1 Hz, CH_3), 3.37(2H, q, J=7.1 Hz, CH_2CH_3), 4.46(2H, s, CH_2I), 7.43 (2H, m, 3,5-Ph-H), 7.96(2H, m, 2,6-Ph-H)

d. *p*-Meth xybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylthio-3-bromo-2-oxoazetidin-1-yl]acetate

A solution of silver (3*S*,4*R*)-3-bromo-1-(*p*-methoxybenzyloxycarbonylmethyl)-2-oxoazetidine-4-thiolate (2.34g, 0.005mol) in acetonitrile (20 ml) was treated with a solution of 4-carbethoxybenzyl iodide (1.74g, 0.006mol) in acetonitrile (10ml) and the mixture stirred in subdued light for 2.5hrs. The mixture was filtered through hyflo, the filtrate evaporated and the residue purified by flash chromatography (silica, ethyl acetate-pet. ether) to give the title compound as a white solid, m.p. 97-9°C, 1.60g (61% yield).
^{1}H NMR δ ($CDCl_3$), 1.39(3H, t, J=7.1Hz, CH_2CH_3), 3.48, 4.07 (each 1H, d, J=18 Hz, NCH_2), 3.80 (5H, s, SCH_2 + OCH_3), 4.37 (2H, q, J=7.1Hz, CH_2CH_3), 4.61, 4.91 (each 1H, d, J=1.6 Hz, H_3 + H_4), 5.03, 5.12 (2H, 2xd, J=11.8Hz, OCH_2), 6.89 (2H, m, 3,5-(4-CH_3OPh)-H), 7.26-7.41 (4H, m, 2,6-(4-CO_2Et)Ph-H + 2,6-(4-CH_3OPh)-H), 8.00 (2H, m, 3,5-(4-CO_2Et)Ph-H).

e. *p*-Methoxybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylsulphinyl-3-bromo-2-oxoazetidin-1-yl]acetate Diast 2:1 75:25

p-Methoxybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylthio-3-bromo-2-oxoazetidin-1-yl]acetate (15.2g, 0.029mol) was dissolved in dichloromethane (400ml), cooled to -65°C and a solution of m-chloroperbenzoic acid (8.9g,0.029mol) in dichloromethane (450 ml) added dropwise with stirring over 20 min. The cooling bath was removed and the mixture stirred at RT for 2hrs. The solution was shaken with a mixture of saturated aqueous sodium sulphite and saturated sodium hydrogen carbonate and the organic layer separated, washed with water, dried ($MgSO_4$) and evaporated to an oil.
Hot ethyl acetate (60ml) was added and after cooling in freezer overnight, p-methoxybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylsulphinyl-3-bromo-2-oxoazetidin-1-yl]acetate crystallised out as a white solid as a 75:25 mixture of diastereomers (2:1), 9.94g, (63% yield)
^{1}H NMR of major component: δ ($CDCl_3$), 1.39(3H, t, J=7.1Hz, CH_2CH_3), 3.80 (3H, OCH_3), 4.0 - 4.2 (3H, m, $SOCH_2$ + NCH_2), 4.3 - 4.4 (3H, m, CH_2CH_3 + NCH_2), 4.50, 4.81 (each 1H, d, J=1.7 Hz, H_3 + H_4), 5.1 (2H, m, OCH_2), 6.88 (2H, m, 3,5-(4-CH_3OPh)-H), 7.26 (2H, m, 2,6-(4-CH_3OPh)-H), 7.41 (2H, m, 2,6-(4-CO_2Et)Ph-H), 8.00 (2H, m, 3,5-(4-CO_2Et)Ph-H).

f. [(4*R*)-4-(4-carbethoxy)benzylsulphinyl-2-oxoazetidin-1-yl]acetic acid Diast 2

p-Methoxybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylsulphinyl-3-bromo-2-oxoazetidin-1-yl]acetate (8.75g, 16.25mmol) was dissolved by warming in ethanol (400ml) and a solution of sodium bicarbonate (4.0g, 48mmol) in water (40ml) was added. To the cloudy mixture was added 10% Pd on carbon (0.5g) and the warm mixture (initial temp 40°C) was hydrogenated at 50psi, room temp for 2 hrs. More catalyst (1.0g) was added, the mixture warmed to 35°C and hydrogenated as above for 2 hrs. The mixture was filtered through hyflo and evaporated to give a mixture of p-methoxybenzyl and ethyl esters of the des-bromo derivative as brown oil. This was dissolved in ethanol (50ml), cooled to 10°C and 1N sodium hydroxide (17ml) was added dropwise over 10min. The mixture was stirred at 10°C for 45mins then most of the ethanol was evaporated off and the residue dissolved in dichloromethane and water. The layers were separated and the aqueous washed with dichloromethane then acidified with conc hydrochloric acid (2ml) and extracted with dichloromethane. The extracts were dried ($MgSO_4$) with the addition of charcoal, filtered through hyflo and evaporated to a black foam. This was dissolved in chloroform and refrigerated overnight. A small amount of solid was filtered off and the filtrate evaporated to a black oil which solidified under ether to give the title compound as an off-white solid, 3.77g, (68% yield) (ratio of dia 2:dia 1 94:6). The chromatographic and spectral characteristics of this material identified it as the same compound prepared in Example 6h.

^{1}H NMR δ (DMSO) 1.32 (3H, t, J=7Hz, CH_3), 2.99 (1H, m, H_3), 3.33 (1H, m, H_3), 3.95 (1H, d, J= 18.2Hz, NCH_2), 4.15 (2H, m, NCH_2 + $SOCH_2$), 4.34 (3H, m, $SOCH_2$ + CO_2CH_2), 4.82 (1H, m, H_4), 7.51 (2H, d, J=8.3Hz, Ph-H), 7.97 (2H, d, J=8.3Hz, Ph-H)

g. [(4*R*)-4-(4-carbethoxy)benzylsulphinyl-2-oxoazetidin-1-yl]acetic acid Diast 2

[(4*R*, *SS*)-4-(4-carbethoxy)benzylsulphinyl-2-oxoazetidin-1-yl]acetic acid (Diast 2) was also prepared by the following procedure: *p*-Methoxybenzyl [(3*S*, 4*R*)-4-(4-carbethoxy)benzylsulphinyl-3-bromo-2-oxoazetidin-1-yl]acetate (Diast 2:1 75:25) (4.59g, 8.52mmol) was dissolved in dichloromethane (50ml), cooled in an ice bath and activated zinc powder (1.11g, 17.05mmol) was added followed by glacial acetic acid (8ml). After 1 hr, the mixture was diluted with dichloromethane-water, and the organic layer washed with saturated aq. $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to an oil which was purified by flash chromatography (silica, ethyl acetate-pet. ether) to give the title compound as an oil which solidified on standing.

h. (+)-4*R*, *SS*-N-(6-(4-Fluorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide

Treatment of [(4*R*)-4-(4-carbethoxy)benzylsulphinyl-2-oxoazetidin-1-yl]acetic acid with 6-(*p*-fluoropheny)lhexylamine under the conditions described for Example 6i gave, after chromatography, the title compound with identical spectral and chromatographic characteristics to that prepared in Example 6i. $a_D^{25°C}$ = +71.9 (c. 1.0% w/v $CHCl_3$, 25°C)

Example 9 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(cyclohexyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (see above, 4 g, 0.00819 mol) and iodomethyl cyclohexyl carbonate (3.49 g. 0.0123 mol) in N-methylpyrrolidinone (40 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (1.7 g, 0.0123 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with 5% aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (fine silica, ethyl acetate) and the title compound obtained as white crystals m.p.105-7°C after trituration with ether/light petrol, 4.16 g, 79% yield

^1H NMR δ (DMSO) 1.23-1.51 (14H, m), 1.64 (2H, m), 1.84 (2H, m), 2.51 (2H, m), 3.04 (3H, m), 3.35 (1H, m), 3.83 and 4.09 (each 1H, d), 4.15 and 4.35 (each 1H, d), 4.58 (1H, m), 4.85 (1H, m), 5.95 (2H, s), 7.05 (2H, m), 7.18 (2H, m), 7.53 (2H, d), 7.98 (2H, d), 8.11 (1H, bt).

Found: C, 61.6; H, 6.4; N,4.6%; $C_{33}H_{41}FN_2O_8S$ requires: C, 61.5; H, 6.4; N, 4.3%

Example 10 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(tert-butyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.2g, 0.00041 mol) and iodomethyl tert-butyl carbonate (0.49 g. 0.001 mol) in N-methylpyrrolidinone (2 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (0.14 g, 0.001 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium sulphite, dried ($MgSO_4$) and evaporated. The residue was crystallised by trituration with light petrol to give the title compound as white crystals m.p.102-4°C, 0.23 g, 92%yield

^{1}H NMR δ (DMSO) 1.25-1.52 (17H, m), 2.50 (2H, m), 3.06(3H, m), 3.35 (1H, m), 3.84 and 4.09 (each 1H, d), 4.15 and 4.35 (each 1H, d), 4.86 (1H, m), 5.90 (2H, s), 7.06 (2H, m), 7.18 (2H, m), 7.53 (2H, d), 7.97 (2H, d), 7.99 (1H, bt)
Found: C, 60.1; H, 6.3; N, 4.7%; $C_{31}H_{39}FN_2O_8S$ requires: C, 60.2; H, 6.4; N, 4.5%

Example 11 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(1-methylcyclohexyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.2g, 0.00041 mol) and chloromethyl 1-methylcyclohexyl carbonate (0.21 g. 0.001 mol) in N-methylpyrrolidinone (2 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (0.14 g, 0.001 mol) and potassium iodide (0.166 g, 0.001 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (fine silica, ethyl acetate) and the material thus obtained crystallised by trituration with ether, to give the title compound as yield white crystals, m.p. 92-3°C, 0.11 g, 41% yield
^{1}H NMR δ (DMSO)1.25-1.48 (16H, m), 2.00 (2H, m), 2.5 (5H, m), 3.07 (3H, m), 3.36 (1H, m), 3.83 and 4.09 (each 1H, d), 4.15 and 4.35 (each 1H, d), 4.86 (1H, m), 5.91 (2H, s), 7.06 (2H, m), 7.18 (2H, m), 7.54 (2H, d), 7,98 (2H, d), 8.11 (1H, bt)

Example 12 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(phenylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (5 g, 0.0102 mol) and benzoyloxychloromethane (2.62 g. 0.0154 mol) in N-methylpyrrolidinone (50 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (2.12 g, 0.0154 mol) and potassium iodide (2.55 g, 0.0154 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (fine silica, ethyl acetate) and the material thus obtained crystallised by trituration with ether to give the title compound as white crystals, m.p.117-9°C, 4 g, 52% yield

^{1}H NMR δ ($CDCl_3$) 1.33 (4H, m), 1.5-1.62 (4H, m), 2.56 (2H, t), 2.95, (1H, dd), 3.22 (3 H, m), 3.94 and 4.20 (each 1H, d), 4.04 and 4.16 (each 1H, d), 4.65 (1H, m), 6.25 (2H, s), 6.94 (3H, m), 7.11 (2H, m), 7.37 (2H, d), 7.46 (2H, m), 7.59 (1H, m), 8.1 (4H, m)
Found: C, 63.7; H,5.5; N, 4.5%; $C_{33}H_{35}FN_2O_7S$ requires:C, 63.7; H, 5.7; N, 4.5%

Example 13 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(4-methoxyphenylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (2 g, 0.0041 mol) and 4-methoxybenzoyloxymethyl chloride (2 g. 0.01 mol) in N-methylpyrrolidinone (20 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (1.38 g, 0.01 mol) and potassium iodide (1.66 g, 0.01 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (fine silica, ethyl acetate) and the material thus obtained crystallised by trituration with ether, then recrystallised from dichloromethane/light petrol, to give the title compound as white crystals, m.p. 115-8°C, 1.34 g, 50% yield
^{1}H NMR δ (DMSO) 1.23-1.6 (8H, m), 2.50 (2H, m), 3.02-3.1(3H, m), 3.34 (1H, m), 3.8 and 4.09 (each 1H, d), 3.84 (3H, s), 4.14 and 4.33 (each 1H, d), 4.85 (1H, m), 6.17 (2H, s), 7.05 (4H, m), 7.16 (2H, m), 7.52 (2H, d), 7.97 (4H, m), 8.1 (1H, bt)

Example 14 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(isobutyryloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.2g, 0.00041 mol) and isobutyryloxymethyl iodide (0.23 g. 0.001 mol) in N-methylpyrrolidinone (2 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (0.14 g, 0.001 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (fine silica, ethyl acetate) and the material thus obtained crystallised by trituration with ether, to give the title compound as white crystals, m.p. 104-6°C, 0.14 g, 58% yield

^{1}H NMR δ (DMSO)1.09 (6H, d), 1.25-1.52 (8H, m), 2.50 (2H, m), 2.61 (1H, m), 2.97-3.06 (3H, m), 3.34 (1H, m), 3.83 and 4.09 (each 1H, d), 4.15 and 4.34 (each 1H, d), 4.84 (1H, m), 5.95 (2H, s), 7.06 (2H, m), 7.16 (2H, m), 7.53 (2H, d), 7.97 (2H, d), 7.99 (1H, bt)

Example 15 - (4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(2-methoxyprop-2-ylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (3 g, 0.00614 mol) and 2-methoxyprop-2-ylcarbonyloxymethyl chloride (1.53 g. 0.00921 mol) in N-methylpyrrolidinone (30 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate 1.27 g, 0.00921 mol) and potassium iodide (1.53 g, 0.00921 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with aq. sodium thiosulphate, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (fine silica, ethyl acetate) and the material thus obtained as a solution in ethyl acetate further washed with aq. sodium thiosulphate then stirred for 10 min with $MgSO_4$ and decolourising charcoal. The solids were filtered off and the filtrate evaporated, and the residue crystallised by trituration with ether/light petrol to give the title compound as white crystals m.p. 92-4°C, 2.6 g, 68% yield

^{1}H NMR δ ($CDCl_3$) 1.34 (4H, m), 1.45 (6H, s), 1.58 (4H, m), 2.56 (2H, t), 2.95 (1H, dd), 3.17-3.37 (3H, m + 3H, s), 3.96 and 4.10 (each 1H, d), 4.05 and 4.22 (each 1H, d), 4.69 (1H, m), 6.06 (2H, s), 6.93 (3H, m), 7.09 (2H, m), 7.39 (2H, d), 8.09 (2H, d)

Example 16 - (4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-((5-methyl-2-oxo-1,3-dioxolen-4-yl)methyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

A solution of (4*R*, *SS*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (5 g, 0.0102 mol) and 4-bromomethyl-5-methyl-1,3-dioxol-2-one (2.96 g. 0.0154 mol) in N-methylpyrrolidinone (50 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (2.12 g, 0.0154 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (fine silica, ethyl acetate) and the material thus obtained

crystallised by trituration with ether/light petrol to give the title compound as white crystals, m.p. 84-7°C, 3.81 g, 62% yield.
^{1}H NMR δ ($CDCl_3$) 1.24-1.54 (8H, m), 2.22 (3H, s), 2.5 (2H, m), 2.95 (1H, dd), 3.05 (2H, m), 3.33 (1H, m), 3.84 and 4.07 (each 1H, d), 4.15 and 4.32 (each 1H, d), 4.85 (1H, m), 5.22 (2H, s), 7.06 (2H, m), 7.18 (2H, m), 7.51 (2H, d), 7.98 (2H, d), 8.1 (1H, bt)
Found: C, 59.7; H, 5.5; N, 4.7%; $C_{30}H_{33}FN_2O_8S$ requires:C, 60.0; H, 5.5; N, 4.7%

Example 17 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-((2-methoxycarbonyl-*E*-but-2-en-yl)methyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide
A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.195 g, 0.0004 mol) and methyl *E*-2-bromomethylbut-2-enoate (0.16 g. 0.0008 mol) in N-methylpyrrolidinone (2 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (0.11 g, 0.0008 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (fine silica, ethyl acetate) and the material thus obtained crystallised by trituration with ether to give the title compound as white microprisms, 0.024 g, 10% yield
^{1}H NMR δ ($CDCl_3$) 1.25-1.63 (8H, m), 1.99(3H, d), 2.56 (2H, t), 2.93 (1H, dd), 3.17-3.36 (3H, m), 3.79 (3H, s), 3.93 and 4.17 (each 1H, d), 3.43 and 4.23 (each 1H, d), 4.64 (1H, m), 5.12 (2H, s), 6.91-7.26 (6H, m), 7.34 (2H, d), 8.04 (2H, d)

Example 18 - (4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(N-N-dimethylaminocarbonylmethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide
A solution of (4*R*, S*S*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (0.2 g, 0.0004 mol) and α-chloro-N,N-dimethyl acetamide (0.17 g. 0.001 mol) in N-methylpyrrolidinone (2 ml, dried over 4A molecular sieves) was treated with anhydrous potassium carbonate (0.14 g, 0.001 mol) and stirred for 16 h at ambient temperature. The mixture was diluted with water and extracted thoroughly with ethyl acetate, and the combined extracts dried ($MgSO_4$) and evaporated. The residue was crystallised by trituration with ether to give the title compound as white cryatals, m.p. 141-4°C, 0.01 g

^{1}H NMR δ ($CDCl_3$) 1.25-1.75 (8H, m), 2.56 (2H, t), 2.93 (1H, dd), 2.99 (3H, s), 3.04 (3H, s), 3.17-3.36 (3H, m), 3.85-4.25 (4H, 4 x d), 4.65 (1H, m), 4.97 (2H, s), 6.93 (2H, m), 7.10 (3H, m), 7.36 (2H, d), 8.13 (2H, d).

Example 19 - (4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(N-N-di-(2-hydroxyethyl)aminocarbonylmethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide

To a solution of N,N-(1,1-dihydroxyethyl)bromoacetamide (1.20g, 5.3mmol) in DMF (10ml) was added (4*R*, *SS*)-N-(6-[4-fluorophenyl]hex-1-yl)-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (1.00g, 2.05mmol) followed by caesium carbonate (1.3g, 4.0mmol). The mixture was stirred for 18 hrs then separated between ethyl acetate and 2M hydrochloric acid. Separation of the organics followed by washing with brine, drying ($MgSO_4$) and concentration provided the crude product as a white solid. The solids were washed with chloroform, filtered and dried to yield the product as a white solid (0.97g, 75%) mp 119-121°C.

^{1}H nmr δ ($DMSO_{D6}$) 1.28-1.55(m,8H), 2.5(t, J=12Hz, 2H), 2.8(br d, J=16Hz, 1H), 3.1(q, J=10Hz, 2H), 3.3-3.7(m, 9H), 3.9(d, J=27Hz, 1H), 4.1(d, J=27Hz, 1H), 4.15(d, J=20Hz, 1H), 4.35(d, J=20Hz, 1H), 4.7(br, 1H), 4.85(m, 1H), 4.95(br, 1H), 5.2(s, 2H), 7.0(apparent t, J=14Hz, 2H), 7.15(dd, J=14, 9Hz, 2H), 7.5(d, J=13Hz, 2H), 8.05(d, J=13Hz, 2H), 8.2(t, J=8Hz, 1H)

Example 20 Enantiomers of *(R,S/S,R)*-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine

a. 6-(4-Fluorophenyl)hexyloxy ethanol

Ethylene glycol (41.26g) and 6-(4-fluorophenyl)hexyl bromide (17.22g) were added to a solution of sodium hydroxide (2.79g) in water (2.5ml) and the mixture was heated at 110°for 24 hours. The mixture was cooled and partitioned between water (150ml) and diethyl ether (150ml). The layers were separated and the organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated to an orange oil. Purification by column chromatography on silica gel eluted with [5:1] to [1:1] P.E 40-60°C:ethyl acetate gave the product as an orange oil (9.91g, 62%).

b. 6-(4-Fluorophenyl)hexyloxy triflate

6-(4-Fluorophenyl)hexyloxy ethanol (4.0g), pyridine (1.43g) and DMAP (40mg) were dissolved in dry dichloromethane (30ml), cooled to -10°C and triflic anhydride (5.6g) in dry dichloromethane (10ml) was added over 5 minutes keeping temperature below 0°C. The mixture was stirred at -10°C to 0°C over 60 minutes and then washed with water (50ml), brine (50ml), dried ($MgSO_4$) and evaporated to a brown oil (6.17g, 99%).

c. 1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarb nylbenzylthio)-2-oxoazetidine

A solution of 6-(4-fluorophenyl)hexyloxy triflate (7.0g), 4-(4-allyloxycarbonylbenztlthio)azetidin-2-one (5.08g) and tetrabutylammonium bromide (0.59g) in dry THF (150ml) was cooled to 15°C under nitrogen and was treated with powdered potassium hydroxide (1.08g). The cooling bath was removed and the reaction was stirred for 30 minutes. Powdered KOH (50mg) was added and the reaction was stirred at room temperature for 30 minutes. The mixture was filtered through celite and washed through with ethyl acetate (100ml). The filtrate was evaporated to a dark oil and purification by flash column chromatography on silica gel eluted with [3:2] to [1:1] P.E. 40-60°C: ethyl acetate gave the product as an orange oil (4.65g, 51%).

1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.55 (2H, t, J = 7.6Hz, CH_2Ph), 2.85, 2.90 (1H, dd, H_3), 3.05 (1H, m, 1H), 3.26, 3.32(1H, dd, J=4.9, 15.1Hz, H_3), 3.37-3.68 (5H, m, NCH_2CH_2, OCH_2), 3.86 (2H, s, SCH_2), 4.76 (1H, m, H_4), 4.81 (2H, m CO_2CH_2), 5.36 (2H, m, CH=CH_2), 6.03 (1H, m, CH=CH_2), 6.94 (2H, m p-FPh-H), 7.07 (2H,m, p-FPh-H), 7.39 (2H, d, J=8.3Hz, Ph-H), 8.01 (2H, d, J=8.3Hz, Ph-H)

d. *(R,S/S,R)*-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast 2)

A solution of 1-(2-(6-fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylthio)-2-oxoazetidine (4.58g) in dichloromethane (100ml), cooled to -70°C, was treated with a solution of mcpba (2.0g) in CH_2Cl_2 (125ml) dropwise over 1 hour maintaining the temperature at below -70°C. The cooling bath was removed and the reaction was stirred for 1.5 hours, washed with a solution of 10% aq.sodium hydrogen carbonate(150ml) + 10% aq. sodium sulphite (150ml). The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil which solidified on standing. Repeat recyrstallisations from diethyl ether (3 times) gave diastereoisomer 2 as a colourless solid (0.7g,12.2%).m.p. 73-74°C

1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2,14.8Hz, H_3), 3.38-3.68 (7H, m, H_3, NCH_2CH_2, OCH_2), 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, CH=CH_2) 6.03 (1H, m, CH=CH_2), 6.94 (2H, m, p-FPh-H), 7.10 (2H, m, p-FPh-H), 7.38 (2H, d, J=8.4Hz, Ph-H), 8.08 (2H, m, Ph-H)

e. *(R,R/S,S)*-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast 1)

A sample of diastereoisomer 1 (contains 21% dia2) was obtained as a colourless solid, m.p.46-50°C.

1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.55 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=4.8,14.8Hz, H_3), 3.38-3.68 (7H, m, H_3, NCH_2CH_2, OCH_2), 3.94 (2H, m, $SOCH_2$), 4.55 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$), 6.94 (2H, m, p-FPh-H), 7.10 (2H, m, p-FPh-H), 7.38 (2H, d, J=8.4Hz, Ph-H), 8.08 (2H, m, Ph-H)

Enantiomers of *(R,S/S,R)*-1-(2-(6-fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine were separated by hplc on a Chiracel OD -20MM eluted with 60:40 ethanol hexane:

f. (+)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast. 2)
164mg, colourless solid. M.p. 52-53°C
Enantiomerically pure
$[\alpha]_D$ = +57.5° (c=0.5%w/v in ethanol at 25°C)
1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2,14.8Hz, H_3), 3.38-3.68 (7H, m, H_3, NCH_2CH_2, OCH_2), 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$), 6.94 (2H, m, p-FPh-H), 7.10 (2H, m, p-FPh-H), 7.38 (2H, d, J=8.4Hz, Ph-H), 8.08 (2H, m, Ph-H)

g. (-) 1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast. 2)
170mg, colourless solid M.p. 51-53°C
99.69% desired enantiomer with 0.31% of the other enantiomer present
$[\alpha]_D$ = -57.9°C (c=0.4%w/v in ethanol at 25°C)
1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2,14.8Hz, H_3), 3.38-3.68 (7H, m, H_3, NCH_2CH_2, OCH_2), 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$), 6.94 (2H, m, p-FPh-H), 7.10 (2H, m, p-FPh-H), 7.38 (2H, d, J=8.4Hz, Ph-H), 8.08 (2H, m, Ph-H)

Example 21 (R,S/S,R)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2)
(R,S/S,R)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (220mg), triphenylphosphine (11mg), tetrakis(triphenylphosphine)palladium (0) (15mg) in dry CH_2Cl_2 (5ml) under nitrogen was treated with pyrrolidine (37µl) and the mixture was stirred at room temperature for 19 hours.. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. The oil was dissolved in CH_2Cl_2 (4ml) and diluted with diethyl

ether (75ml), washed with water, brine, dried ($MgSO_4$), filtered and evaporated to an oil which solidified on cooling. Trituration with diethyl ether gave the product as a cream solid (155mg, 78%) m.p.95-96°C
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J=7.6Hz, CH_2Ph), 2.69, 2.76,(1H, dd, J=2.1,15.1Hz, H_3), 3.10, 3.17 (1H, dd, J=5.1, 15.1Hz), 3.37-3.74 (6H,m, NCH_2CH_2, OCH_2), 4.11 (2H, s, $SOCH_2$), 4.64 (1H, m, H_4), 6.94 (2H, m, p-FPh-H), 7.10 (2H, m, p-FPh-H), 7.41 (2H, d, J=8Hz, Ph-H), 8.07 (2H, d, J=8Hz, Ph-H)

Example 22 (-)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2)
(-)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (145mg), triphenylphosphine (7.3mg), tetrakis(triphenylphosphine)palladium (0) (10.5mg) in dry CH_2Cl_2 (4ml) under nitrogen was treated with pyrrolidine (23.5µl) and the mixture was stirred at room temperature for 6 hours. Pyrrolidine (5µl) was added and the reaction was stirred at room temperature for 19 hours. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the title compound as an oil. Trituration with diethyl ether gave the product as a cream solid (113mg, 85%) m.p.123-124°C, $[\alpha]_D$ = -53.5° (c=0.5 %w/v in ethanol at 25°C)
1H NMR δ (DMSO) 1.25-1.6 (8H, m, 4xCH_2,), 2.50 (2H, t, CH_2Ph), 2.91, 2.95 (1H, dd, J=2,15.2Hz, H_3), 3.22-3.53 (7H,m, H_3, NCH_2CH_2, OCH_2), 4.16, 4.31 (each 1H, 2xd, J=13Hz, $SOCH_2$), 4.73 (1H, m, H_4), 7.0 (2H, m, p-FPh-H), 7.19 (2H, m, p-FPh-H), 7.48 (2H, d, J=8Hz, Ph-H), 7.94 (2H, d, J=8Hz, Ph-H)

Example 23 (+)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2)
(+)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (140mg), triphenylphosphine (7mg), tetrakis(triphenylphosphine)palladium (0) (10mg) in dry CH_2Cl_2 (4ml) under nitrogen was treated with pyrrolidine (23.5µl) and the mixture was stirred at room temperature for 19 hours. 1.5mg more catalyst and pyrrolidine (5µl) were added and the reaction was stirred for 2 hours, diluted with water (25ml) and CH_2Cl_2 (25ml) and acidified to pH 2 with HCl (2N). The layers were separated and the aquoues layer was washed with CH_2Cl_2 (25ml) The organic extracts were combined, dried ($MgSO_4$) and evaporated to a yellow oil. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. Trituration with diethyl ether gave the

product as a colourless solid (109mg, 84%) m.p.118-120°C, $[\alpha]_D$ = +50.0° (c=0.5%w/v in ethanol at 25°C)
1H NMR δ (DMSO) 1.25-1.6 (8H, m, 4xCH_2,), 2.50 (2H, t, CH_2Ph), 2.91, 2.95 (1H, dd, J=2,15.2Hz, H_3), 3.22-3.53 (7H,m, H_3, NCH_2CH_2, OCH_2), 4.16, 4.31 (each 1H, 2xd, J=13Hz, $SOCH_2$), 4.73 (1H, m, H_4), 7.0 (2H, m, p-FPh-H), 7.19 (2H, m, p-FPh-H), 7.48 (2H, d, J=8Hz, Ph-H), 7.94 (2H, d, J=8Hz, Ph-H)

Example 24 Enantiomers of *(R,S/S,R)*-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine

a. 6-(4-Chlorophenyl)hexyloxy ethanol

Ethylene glycol (51.1g) and 6-(4-chlorophenyl)hexyl bromide (22.7g) were added to a solution of sodium hydroxide (3.46g) in water (3.1ml) and the mixture was heated at 110°for 24 hours. The mixture was cooled and partitioned between water (300ml) and diethyl ether (300ml). The layers were separated and the aqueous layer was washed with ether (150ml). The organic layers were combined and washed with water, brine, dried ($MgSO_4$) and evaporated to yellow oil. Purification by column chromatography on silica gel eluted with [3:1] to [2:1] P.E 40-60°C:ethyl acetate gave the product as a yellow oil (14.13g, 67%).

b. 6-(4-Chlorophenyl)hexyloxy triflate

6-(4-Chlorophenyl)hexyloxy ethanol (7.6g), pyridine (2.53g) and DMAP (79mg) were dissolved in dry dichloromethane (60ml), cooled to -10°C and triflic anhydride (10.0g) in dry dichloromethane (20ml) was added over 7 minutes keeping T below 0°C. The mixture was stirred at 0°C for 45 minutes, washed with water (60ml), brine (60ml), dried ($MgSO_4$) and evaporated to a dark oil (11.13g, 97%).

c. (2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylthio)-2-oxoazetidine

A solution of 6-(4-chlorophenyl)hexyloxy triflate (11.1g), 4-(4-allyloxycarbonylbenzylthio)azetidin-2-one (7.69g) and tetrabutylammonium bromide (0.89g) in dry THF (200ml) was cooled to 10°C under nitrogen and was treated with powdered potassium hydroxide (1.63g). The cooling bath was removed and the reaction was stirred for 40 minutes. Powdered KOH (163mg) was added and the reaction was stirred at room temperature for 1.5h, partitioned between brine (600ml) and ethyl acetate (400ml). The mixture was filtered through hy-flo and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated to a dark oil. Purification by flash column chromatography on silica gel eluted with [2:1] to [1:1] P.E. 40-60°C: ethyl acetate gave the product as an orange oil (7.28g, 51%).
1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.55 (2H, t, J = 7.6Hz, CH_2Ph), 2.85, 2.90 (1H, dd, H_3), 3.05 (1H, m, 1H), 3.26, 3.32(1H, dd, J=4.9, 15.1Hz,

H_3), 3.37-3.68 (5H, m, NCH_2CH_2, OCH_2), 3.86 (2H, s, SCH_2), 4.76 (1H, m, H_4), 4.81 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$) 7.07 (2H, d, J=8.4Hz, p-ClPh-H), 7.23 (2H,m, p-ClPh-H), 7.39 (2H, d, J=8.3Hz, Ph-H), 8.01 (2H, d, J=8.3Hz, Ph-H)

d. *(R,S/S,R)*-1-(2-(6-Chlorophenyl)hexyl xy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine

A solution of 1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylthio)-2-oxoazetidine (7.2g) in dichloromethane (175ml), cooled to -70°C, was treated with a solution of mcpba (3.0g) in CH_2Cl_2 (175ml) dropwise over 1 hour maintaining the temperature at below -70°C. The cooling bath was removed and the reaction was stirred for 1.5 hours, washed with a solution of 10% aq.sodium hydrogen carbonate(200ml) + 10% aq. sodium sulphite (200ml). The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil which solidified on standing. Repeat recyrstallisations from diethyl ether (4 times) gave diastereoisomer 2 as a colourless solid (0.9g,12.2%).

1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2.4,15.2Hz, H_3), 3.07, 3.11 (1H, dd, J=4.8, 15.2Hz, H_3), 3.37-3.68 (6H, m, NCH_2CH_2, OCH_2), 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$) 7.09 (2H, d, J=8.8Hz, p-ClPh-H), 7.23 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8.4Hz, Ph-H), 8.07 (2H, m, Ph-H)

The above racemic compound was separated by hplc on a Chiracel OD -20mm eluted with 80:20 ethanol:hexane to give the enantiomers:

e. (+)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine

83mg, colourless solid. M.p. 57-59°C

99.95% desired enantiomer with 0.05% of the other enantiomer present

$[\alpha]_D$ = +52.2° (c=0.28%w/v in ethanol at 25°C)

1H NMR δ ($CDCl_3$) 1.3-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2.4,15.2Hz, H_3), 3.07, 3.11 (1H, dd, J=4.8, 15.2Hz, H_3), 3.37-3.68 (6H, m, NCH_2CH_2, OCH_2), 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, $CH=CH_2$) 6.03 (1H, m, $CH=CH_2$) 7.09 (2H, d, J=8.8Hz, p-ClPh-H), 7.23 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8.4Hz, Ph-H), 8.07 (2H, m, Ph-H)

f. (-)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine

103mg colourless solid M.p. 58-59°C

99.62% desired enantiomer with 0.38% of the other enantiomer present $[\alpha]_D$ = -61.9°C (c=0.06%w/v in ethanol at 25°C)
1H NMR δ ($CDCl_3$) 1.2-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.66, 2.69 (1H, dd, J=2.4,15.2Hz, H_3), 3.07, 3.11 (1H, dd, J=4.8, 15.2Hz, H_3), 3.37-3.68 (6H, m, NCH_2CH_2, OCH_2, 4.07 (2H, s, $SOCH_2$), 4.54 (1H, m, H_4), 4.83 (2H, m CO_2CH_2), 5.36 (2H, m, CH=CH_2) 6.03 (1H, m, CH=CH_2) 7.09 (2H, d, J=8.8Hz, p-ClPh-H), 7.23 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8.4Hz, Ph-H), 8.07 (2H, m, Ph-H)

Example 25 (-)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2)
(-)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (86.2mg), triphenylphosphine (4.2mg), tetrakis(triphenylphosphine)palladium (0) (6mg) in dry CH_2Cl_2 (2ml) under nitrogen was treated with pyrrolidine (13.5µl) and the mixture was stirred at room temperature for 19 hours. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. Trituration with diethyl ether gave the title compound as a cream solid (59.8mg, 75%) m.p.102-102°C, $[\alpha]_D$ = -37.32° (c=0.209%w/v in ethanol at 25°C)
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.6Hz, CH_2Ph), 2.71, 2.74 (1H, dd, J=2,15Hz, H_3), 3.12, 3.15 (1H, dd, J=5.2, 15Hz, H_3), 3.38-3.72 (6H, m, NCH_2CH_2, OCH_2), 4.09 (2H, m, $SOCH_2$), 4.60 (1H, m, H_4), 7.09 (2H, d, J=8.8Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.40 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Example 26 (+)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2)
(+)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (65.6mg), triphenylphosphine (3.2mg), tetrakis(triphenylphosphine)palladium (O) (4.6mg) in dry CH_2Cl_2 (2ml) under nitrogen was treated with pyrrolidine (10.3µl) and the mixture was stirred at room temperature for 19 hours. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. Azeotroping with water and acetone followed by trituration with diethyl ether gave the product as a cream solid (44.7mg, 73%) m.p.104-105°C, $[\alpha]_D$ = +51.92° (c=0.208%w/v in ethanol at 25°C)
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.6Hz, CH_2Ph), 2.71, 2.74 (1H, dd, J=2,15Hz, H_3), 3.12, 3.15 (1H, dd, J=5.2, 15Hz, H_3), 3.38-3.72 (6H, m, NCH_2CH_2, OCH_2), 4.09 (2H, m, $SOCH_2$), 4.60 (1H, m, H_4), 7.09

(2H, d, J=8.8Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.40 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Example 27 (α-S, *4*-R, *S*-S)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide

a. R-Methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate

A suspension of R-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetic acid (from Example 1f, 21.55g) and anhydrous potassium carbonate (8.88g)in 1-methyl-2-pyrrolidinone (100ml) was treated with methyl iodide (10.94g) and the mixture was stirred for 2h. Methyl iodide (1.0g) was added and after 30 minutes the reaction was partitioned between brine (500ml) and diethyl ether (500ml). The layers were separated and the aqueous layer was washed with diethyl ether (500ml). The organic extracts were combined washed with water (x2), brine, dried ($MgSO_4$) and evaporated to an orange oil. Purification by flash column chromatography on silica gel eluted with [1:1] P.E 40-60°C:ethyl acetate gave the title compound as a yellow oil (contains 2% dimethyl ester) (20.0g, 89%).
1H NMR δ ($CDCl_3$) 2.94, 3.01 (1H, dd,J= 2.1, 15.2Hz, H_3), 3.25 (1H, d, J=18Hz, 1 of NCH_2), 3.39, 3.45 (1H, dd, J=5.1, 15.2Hz, H_3), 3.70 (3H, s, CH_3),3.81 (2H, s, SCH_2), 4.04 (1H, d, J=18Hz, 1 of NCH_2), 4.83 (2H, m, CO_2CH_2), 4.93 (1H, m, 4H), 5.35 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 7.39 (2H, d, J=8Hz, Ph-H), 8.02 (2H, d, J=8Hz, Ph-H)

b. α-R,*4*-R-Methyl 2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionate and α-S,*4*-R-Methyl 2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionate

A solution of R-methyl-4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetate (13.2g) in dry tetrahydrofuran (250ml) at -75°C under nitrogen was treated with a 1M solution of lithium bis(trimethylsilyl)amide in THF (46.3ml) over 10 minutes keeping the temperature below -70°C. 1,3-Dimethylimidazolidin-2-one (30.5ml) was added keeping the temperature below -70°C. The resulting suspension was stirred at -75°C for 30 minutes and then treated with methyl iodide (4.3ml) over 1 minute and the temperature rose to -68°C. The reaction was stirred for 1.5 hours at -75°C and then allowed to warm to -20°C over 30 minutes. The reaction was cooled to -75°C and quenched with glacial acetic acid (3.5ml), partitioned between water (300ml) and diethyl ether (250ml). The layers were separated and the aqueous layer was washed with diethyl ether (250ml). The organic extracts were combined washed with brine (x3), dried ($MgSO_4$), and evaporated to a coloured oil. Ratio of 50% R,R (diaA): 15% starting material :35% S,R (dia B). Repeat purification by flash column chromatography on silica gel eluted with P.E. 40-60°C:ethyl acetate gave the products as coloured oils.

R,R Diastereoisomer (A), 3.91g (29%) (contains 9% dia B)
1H NMR δ ($CDCl_3$) 2.9 (1H, dd, H_3), 3.30 (1H, H_3), 3.75 (3H, s, CH_3),3.88 (2H, s, SCH_2), 4.4 (1H, m, CH), 4.83 (2H, m, CO_2CH_2), 4.90 (1H, m, 4H), 5.35 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 7.39 (2H, d, J=8Hz, Ph-H), 8.02 (2H, d, J=8Hz, Ph-H)
S,R Diastereoisomer (B), 5.36g (39%) (contains some sm and 43% dia A)
1H NMR δ ($CDCl_3$) 2.86, 2.92 (1H, dd, J=2.4, 15.2Hz, H_3), 3.28, 3.33 (1H,dd, J=5.1, 15.2Hz, H_3), 3.73 (3H, s, CH_3),3.85 (2H, s, SCH_2), 3.95 (1H, m, CH), 4.71 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 4.90 (1H, m, 4H), 5.35 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 7.40 (2H, d, J=8Hz, Ph-H), 8.02 (2H, d, J=8Hz, Ph-H)

c. α-S,*4*-R-2-4{4-[(4-Allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionic acid

A solution of methyl 2-{4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl}propionate (2.65g) (mixture of 5% dia A (R,R): 27% dia B (S,R): 65 % desαMe) in THF (50ml) at 3°C was treated with a 1N sodium hydroxide solution (7.5ml) over 60 minutes. The cooling bath was removed and the reaction was stirred for 30 minutes. 1N NaOH (1.0ml) was added over 30 minutes and the reaction was then stirred for 30 minutes, diluted with brine (75ml) and extracted with diethyl ether (75ml). The aqueous layer was acidified with 1NHCl and extracted with diethyl ether (2x75ml). The organic extracts were combined washed with brine, dried ($MgSO_4$), and evaporated to give the title compound as an orange oil (2.5g, 98%).and as a mixture in 5%R,R : 27%R,S : 65% des αMe.

d. α-S,*4*-R-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide

6-(4-Fluorophenyl)hexylamine (1.55g) in dry DMF (50ml) was added to a mixture of 2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionic acid (2.70g) (above), 1-hydroxybenzotriazole (0.95g), N,N'-dicyclohexylcarbodiimide (1.46g) and the mixture was stirred at room temperature for 4h. The suspension was diluted with diethyl ether (100ml) and filtered to remove urea. The filtrate was washed saturated aq.NaHCO3, brine, dried ($MgSO_4$), and evaporated to an oil. Purification by flash column chromatography on silica gel eluted with [2:1] P.E.40-60°C:ethyl acetate gave the product α-S, *4*-R diastereoisomer (B)(contains 10% dia A) as a yellow oil (0.497g,13.4%).
^{1}H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.89 (1H, dd, H_3), 3.25 (3H, m, NCH_2, H_3), 3.86 (2H, s, SCH_2), 4.10 (1H, m, CH), 4.69 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 6.45 (1H, m, NH), 6.94 (2H, m, p-FPh-H), 7.09 (2H, m, p-FPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.028 (2H, m, Ph-H)

Diastereoisomer A was also isolated
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.78, 2.85 (1H, dd, J=2.3, 15.4Hz, H_3), 3.25 (3H, m, NCH_2, H_3), 3.89 (2H,m, SCH_2), 4.05 (1H, m, CH), 4.81 (3H, 4, CO_2CH_2), 5.4 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 6.48 (1H, m, NH), 6.94 (2H, m, p-FPh-H), 7.09 (2H, m, p-FPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.02 (2H, d, Ph-H)

e. α-S,*4*-R,*S*-S-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide

A solution of S,R-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide (1.20g)(80:20 DiaB:A) in dichloromethane (25ml), cooled to -75°C, was treated with a solution of mcpba (0.71g) in CH_2Cl_2 (25ml) over 1 hour keeping the temperature at -75°C. The cooling bath was removed and the reaction was stirred for 2 hours, diluted with CH_2Cl_2 (25ml), washed with 10%aq. sodium sulphite (50ml), sat.$NaHCO_3$ (50ml),dried ($MgSO_4$) and evaporated to a coloured oil.
Purification by flash column chromatography on silica gel eluted with ethyl acetate gave the title compound as a 60:40 mixture of dia B2 (α-S, *4*-R, *S*-S):dia B1(α-S,*4*-R,*S*-R)
Purification on Kromasil 5μm silica (250mmx4.6mm) eluted with 50% hexane: 40% ethanol: 10% $CHCl_3$ gave the title compound Diastereoisomer B2 : (α-S, *4*-R, *S*-S)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide as a colourless oil.
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.89 (1H, dd,J= 2, 15Hz, H_3), 3.24 (3H, m, NCH_2, H_3), 4.02 (2H, m, $SOCH_2$), 4. 44 (1H, m, CH), 4.60 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, $CH=CH_2$), 6.04 (1H, m, $CH=CH_2$), 6.85 (1H, m, NH), 6.94 (2H, m, p-FPh-H), 7.09 (2H, m, p-FPh-H), 7.37 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Example 28 (α-S, *4*-R, *S*-S)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide

A solution of (α-S, *4*-R, *S*-S)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide (dia B2) (240mg),triphenylphosphine (6mg),tetrakis(triphenylphosphine)palladium (O) (15mg) in dry CH_2Cl_2 (5ml) under nitrogen was treated with pyrrolidine (39μl) and the mixture was stirred at room temperature for 19 hours. The mixture was diluted with CH_2Cl_2 (50ml) and water (25ml) and acidified with 2NHCl. The layers were separated and the aqueous was washed with CH_2Cl_2 (2x50ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a yellow gum.
Purification by flash column chromatography on silica gel eluted with a

CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. The oil was dissolved in CH_2Cl_2 (4ml) and diluted with diethyl ether (75ml), washed with water, brine, dried ($MgSO_4$), filtered and evaporated to a brown foam (123mg, 56%)
[α]= No significant optical rotation (c=1.1%w/v in $CHCl_3$)
^1H NMR δ ($CDCl_3$) 1.32-1.6 (13H, m, CH_3, 4xCH_2), 2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.84, 2.88 (1H, dd, J=2.4, 15.2Hz, H_3), 3.1-3.3 (3H, m, $NHCH_2$, H_3), 4.04, 4.10 (2H, 2xd, J=13Hz, $SOCH_2$), 4.4 (1H, q, $CHCH_3$), 4.68 (1H, m, H_4), 6.94 (3H, m, NH, p-F-Ph-H), 7.10 (2H, m, p-F-Ph-H), 7.39 (2H, m, Ar-H), 8.06 (2H, m, Ar-H)

Example 29 (α-R, *4*-R, *S*-R)- and (α-R, *4*-R, *S*-S)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide

A solution of (α-R, *4*-R)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide (1.25g)(diastereoisomer A) in dichloromethane (25ml), cooled to -75°C, was treated with a solution of mcpba (0.75g) in CH_2Cl_2 (25ml) over 1 hour keeping the temperature at -75°C. The cooling bath was removed and the reaction was stirred for 2 hours, diluted with CH_2Cl_2 (50ml), washed with 10%aq. sodium sulphite (50ml), sat.$NaHCO_3$ (50ml), water, dried ($MgSO_4$) and evaporated to a coloured oil. The oil was dissolved in ethyl acetate (7.5ml) and cooled. The resulting solid was collected, washed with diethyl ether and dried to give (α-R, *4*-R, *S*-R)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide (dia A1) as a colourless solid 0.125g,9.7%. The filtrate was purified by flash column chromatography on silica gel eluted with ethyl acetate: P.E. 40-60°C. Pure R,R,R fractions were combined and recrystallised from ethyl acetate/diethyl ether to give R,R,R-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide as a colourless solid (0.195g, 15%), m.p.139-140°C:
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.56 (2H, t, J=7.6Hz, CH_2Ph), 2.79, 2.83 (1H, dd,J= 5, 15Hz, H_3), 3.20 (2H, m, NCH_2), 3.33, 3.39 (1H, dd,J= 2, 15Hz, H_3), 3.94 (2H, m, $SOCH_2$), 4.16 (1H, m, CH), 4.77 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, $CH{=}CH_2$), 6.04 (1H, m, $CH{=}CH_2$), 6.72 (1H, m, NH), 6.94 (2H, m, p-FPh-H), 7.09 (2H, m, p-FPh-H), 7.37 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)
Impure R,R,S fractions were combined and recrystallised from ethyl acetate/diethyl ether to give (α-R, *4*-R, *S*-S)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-

allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide as a colourless solid (0.204g,15.8%), m.p. 102°C:
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.56 (2H, t, J=7.6Hz, CH_2Ph), 2.83 (1H, dd, H), 3.20 (3H, m, NCH_2, H), 4.10 (3H, m, $SOCH_2$, CH), 4.65 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, CH=CH_2), 6.04 (1H, m, CH=CH_2), 6.94 (2H, m, p-FPh-H), 7.09 (2H, m, , NH, p-FPh-H), 7.37 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

In an analagous manner the following chloro compounds were prepared from racemic 4-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylacetic acid.

Example 30 (-)-(α-S, *4*-R, *S*-S)- and (+)-(α-R, *4*-S, *S*-R)-N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide

a. N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-ylpropionamide

A mixture of methyl-2-[(4-allyloxycarbonyl)benzylthio]-2-oxoazetidin-1-yl]propionate(4.87g), hydroxybenzotriazole (1.88g), DCC (2.89g) in dry DMF (60ml) was treated with 6-(4-chlorophenyl)hexylamine and stirred at room temperature for 6 days. The orange suspension was diluted with diethyl ether (200ml) and filtered to remove precipitate. Filtrate was washed with dil $NaHCO_3$ (200ml), brine, dried ($MgSO_4$), and evaporated to an orange oil. Repeat flash column chromatography on silica gel using P.E 40-60°C:ethyl acetate gave :
Diastereoisomer A (R,R/S,S) (0.81g,11%)
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.85 (1H, dd, H), 3.25 (3H, m, NCH_2, H), 3.89 (2H,m, SCH_2), 4.05 (1H, m, CH), 4.81 (3H, 4, CO_2CH_2), 5.4 (2H, m, CH=CH_2), 6.04 (1H, m, CH=CH_2), 6.48 (1H, m, NH), 7.07 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, Ph-H)
Diastereoisomer B (R,S/S,R) (1.63g, 22%)
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.89 (1H, dd, J= 2.3, 15.3Hz, H), 3.25 (3H, m, NCH_2, H), 3.86 (2H, s, SCH_2), 4.10 (1H, m, CH), 4.69 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, CH=CH_2), 6.04 (1H, m, CH=CH_2), 6.43 (1H, m, NH), 7.07 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, m, Ph-H)

b. N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide

A solution of (R,S/S,R)-N-[6-(4-chlorophenyl)hexyl]-2-((4-allyloxycarbonyl)-4-benzylthio)-2-oxoazetidin-1-ylpropionamide (1.60g)(diastereoisomer B) in

dichloromethane (30ml), cooled to -75°C, was treated with a solution of mcpba (0.92g) in CH_2Cl_2 (30ml) over 45 minutes keeping the temperature below -70°C. The cooling bath was removed and the reaction was stirred for 45 minutes, diluted with CH_2Cl_2 (20ml), washed with 10%aq. sodium sulphite (50ml), sat.$NaHCO_3$ (50ml), dried ($MgSO_4$) and evaporated to give the title compound as a mixture of stereoisomers as a coloured oil.(1.6g, 100%). (65%:35% sulfoxide diastereoisomer B2:B1) This material was separated by hplc: Sulfoxide dia B2 was separated from dia B1 using Beckman silica 15cm x 4.6mm eluted with 10:90 ethanol:hexane and subsequent enantiomer separation of diasteroisomer B2 used Chiracel OD-4.6mm eluted with 25:75 ethanol:hexane.

c. (-)-(α-S, *4*-R, *S*-S)-N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide ((-)B2)

Enantiomerically pure, colourless oil, 148mg, $[\alpha]_D$= -4.2° (c=0.4%w/v in $CHCl_3$)
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.89 (1H, dd,J= 2.4, 15.3Hz, H_3), 3.24 (3H, m, NCH_2, H_3), 4.08 (2H, m), 4.60 (1H, m, CH), 4.69 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, CH=CH_2), 6.04 (1H, m, CH=CH_2), 6.95 (1H, m, NH), 7.08 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

d. (+)-(α-R, *4*-S, *S*-R)-N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide ((+)B2)

Sample contains 0.83% of the other enantiomer, colourless oil,145mg, $[\alpha]_D$= +4.3° (c=0.4%w/v in $CHCl_3$)
1H NMR δ ($CDCl_3$) 1.25-1.7 (11H, m, 4xCH_2, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.83, 2.89 (1H, dd,J= 2.4, 15.3Hz, H_3), 3.24 (3H, m, NCH_2, H_3), 4.08 (2H, m), 4.60 (1H, m, CH), 4.69 (1H, m, 4H), 4.83 (2H, m, CO_2CH_2), 5.4 (2H, m, CH=CH_2), 6.04 (1H, m, CH=CH_2), 6.95 (1H, m, NH), 7.08 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Example 31 (-)-(α-S, *4*-R, *S*-S)-[6-(4-Chlorophenyl)hexyl]-2-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide

A solution of (-)-(α-S, *4*-R, *S*-S)-N-[6-(4-chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide (125mg), triphenylphosphine (6mg), tetrakis(triphenylphosphine)palladium (0) (8mg) in dry CH_2Cl_2 (2ml) under nitrogen was treated with pyrrolidine (19.5μl) and the mixture was stirred at room temperature for 19 hours. Purification by flash column chromatography eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. The oil was dissolved in CH_2Cl_2 (2ml) and diluted with diethyl ether (50ml), washed with, brine (x2), dried ($MgSO_4$),

filtered and evaporated to givee the title compound as a yellow foam (104mg, 87%)
$[\alpha]_D$= -3.7° (c=0.5%w/v in $CHCl_3$)
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 1.62 (3H, d, J=7.2Hz, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.86, 2.89 (1H, dd, J=2.4, 15.2Hz,H_3), 3.20 (3H, m, NCH_2, H_3), 4.06 (2H, m, $SOCH_2$), 4.45 (1H, m, CH), 4.66 (1H, m, 4H), 6.95 (1H, m, NH), 7.08 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Example 32 (+)-(α-R, *4*-S, *S*-R)-N-[6-(4-Chlorophenyl)hexyl]-2-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide
A solution of (+)-(α-R, *4*-S, *S*-R)-N-[6-(4-chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide (123mg), triphenylphosphine (6mg), tetrakis(triphenylphosphine)palladium (O) (8mg) in dry CH_2Cl_2 (2ml) under nitrogen was treated with pyrrolidine (19.5µl) and the mixture was stirred at room temperature for 19 hours. Purification by flash column chromatography eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. The oil was dissolved in CH_2Cl_2 (2ml) and diluted with diethyl ether (50ml), washed with, brine (x2), dried ($MgSO_4$), filtered and evaporated to a yellow foam (101mg, 89%)
$[\alpha]_D$= +3.3° (c=0.3%w/v in $CHCl_3$)
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 1.62 (3H, d, J=7.2Hz, CH_3),2.55 (2H, t, J=7.6Hz, CH_2Ph), 2.88 (1H, dd, H_3), 3.20 (3H, m, NCH_2, H_3), 4.06 (2H, m, $SOCH_2$), 4.45 (1H, m, CH), 4.69 (1H, m, 4H), 6.95 (1H, m, NH), 7.08 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

The following racemic compounds were also prepared. These may then be separated into enantiomers by hplc, using a chiral stationary phase, in a similar manner to separations hereinbefore described.

Description 1 *(R,S/S,R)*-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast 2)
(R,S/S,R)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (220mg), triphenylphosphine (11mg), tetrakis(triphenylphosphine)palladium (0) (15mg) in dry CH_2Cl_2 (5ml) under nitrogen was treated with pyrrolidine (37µl) and the mixture was stirred at room temperature for 19 hours. Purification by flash column chromatography on silica gel eluted with a CH_2Cl_2:acetone:acetic acid gradient elution gave the product as an oil. The oil was dissolved in CH_2Cl_2 (4ml) and diluted with diethyl

ether (75ml), washed with water, brine, dried ($MgSO_4$), filtered and evaporated to an oil which solidified on cooling. Trituration with diethyl ether gave the title compound as a cream solid (149mg, 75%) m.p.107-108°C
1H NMR δ ($CDCl_3$) 1.25-1.6 (8H, m, 4xCH_2,), 2.56 (2H, t, J = 7.8Hz, CH_2Ph), 2.71, 2.74 (1H, dd, J=2,15.2Hz, H_3), 3.12, 3.15 (1H, dd, J=5.2, 15.2Hz, H_3), 3.38-3.72 (6H, m, NCH_2CH_2, OCH_2), 4.10 (2H, m, $SOCH_2$), 4.63 (1H, m, H_4), 7.09 (2H, d, J=8.8Hz, p-ClPh-H), 7.22 (2H, d, J=8.8Hz, p-ClPh-H), 7.40 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

Description 2 *(R,S/S,R)*-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast 2)

a. 1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-ethoxycarbonylbenzylthio)-2-oxoazetidine

A solution of 6-(4-chlorophenyl)hexyloxy triflate (3.62g), 4-(4-ethoxycarbonylbenzylthio)azetidin-2-one (2.47g) and tetrabutylammonium bromide (0.30g) in dry THF (70ml) was cooled to 10°C under nitrogen and was treated with powdered potassium hydroxide (0.62g). The cooling bath was removed and the reaction was stirred for 2 hours . The mixture was partitioned between brine (200ml) and ethyl acetate (200ml) and filtered through celite. The layers were separated and the aqueous was washed with ethyl acetate (100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a dark oil. Purification by flash column chromatography on silica gel eluted with [2:1] to [1:1] P.E. 40-60°C: ethyl acetate gave the title compound as a yellow oil (2.41g, 51%).
1H NMR δ ($CDCl_3$) 1.25-1.6 (11H, m, CH_3, 4xCH_2,), 2.55 (2H, t, J =7.6Hz, CH_2Ph), 2.85 (1H, dd, H_3), 3.05 (1H, m), 3.25, 3.30 (1H, dd, H_3), 3.36-3.72 (5H, m, NCH_2CH_2, OCH_2), 3.85 (2H, s, SCH_2), 4.37 (2H, q, J=7.1Hz, CO_2CH_3) 4.76 (1H, m, H_4), 7.07 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, m, p-ClPh-H), 7.39 (2H, d, J=8Hz, Ph-H), 8.08 (2H, d, J=8Hz, Ph-H)

b. *(R,S/S,R)*-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast 2)

A solution of 1-(2-(6-chlorophenyl)hexyloxy)ethyl-4-(4-ethoxycarbonylbenzylthio)-2-oxoazetidine (2.37g) in dichloromethane (75ml), cooled to -70°C, was treated with a solution of mcpba (1.0g) in CH_2Cl_2 (75ml) dropwise over 1 hour maintaining the temperature at below -70°C. The cooling bath was removed and the reaction was stirred for 2 hours, washed with a solution of 10% aq.sodium hydrogen carbonate(50ml) + 10% aq. sodium sulphite (50ml). The layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Recrystallisation from diethyl ether (40ml) gave a colourless solid (0.91g). Purification by flash column chromatography

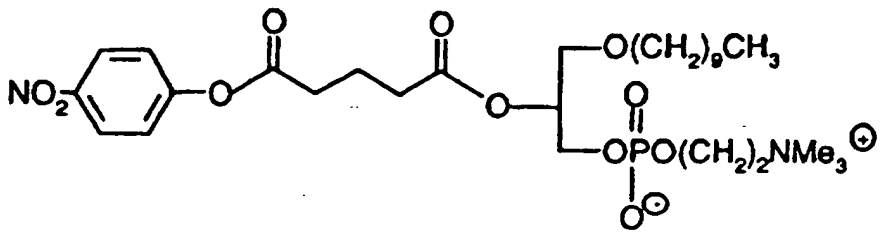
eluted on silica gel with [2:1] ethyl acetate:hexane and recystallisation of the less polar product from diethyl ether (15ml) gave diastereoisomer 2 as a colourless solid (0.40g,16%).m.p. 81-82°C

1H NMR δ ($CDCl_3$) 1.25-1.6 (11H, m, CH_3, 4xCH_2,), 2.55 (2H, t, J =7.8Hz, CH_2Ph), 2.63, 2.69 (1H, dd, J=2.2, 15.1Hz, H_3), 3.05, 3.11 (1H, dd, J=5.1, 15.1Hz, H_3), 3.36-3.74 (6H, m, NCH_2CH_2, OCH_2), 3.75 (2H, s, $SOCH_2$), 4.39 (2H, q, J=7.1Hz, CO_2CH_3) 4.54 (1H, m, H_4), 7.09 (2H, d, J=8.4Hz, p-ClPh-H), 7.22 (2H, m, p-ClPh-H), 7.37 (2H, d, J=8.3Hz, Ph-H), 8.06 (2H, m, Ph-H)

Biological Data

1. Screen for Lp-PLA$_2$ inhibition.

Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

Assays were performed in 96 well titre plates.

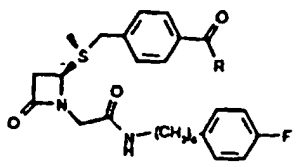
Lp-PLA$_2$ was partially purified by density gradient centrifugation of human plasma. Active fractions were pooled and used as the source of Lp-PLA$_2$. The enzyme was pre-incubated at 37 °C with vehicle or test compound for 10 min in a total volume of 180 µl. The reaction was then initiated by the addition of 20 µl 10x substrate (A) to give a final substrate concentration of 20 µM. The reaction was followed at 405 nm for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

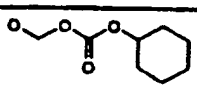
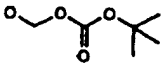
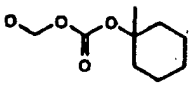
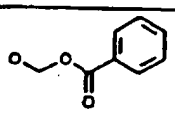
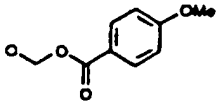
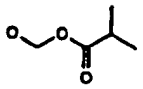
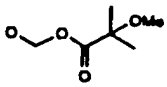
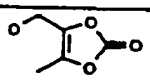
Results:

The compounds of Examples 1 and 2, the corresponding carboxylic acid (+/-)-N-[6-(4-chlorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide and the carboxylic acid (4*R*, *SS*)-N-[6-(4-fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide had IC$_{50}$ values in the range 4 to 20 nM. The compounds of Example 12,13 and 14 had IC$_{50}$ values in the range 2 to 4 nM.

2. Evaluation of Bioavailability

The pro-drug esters were evaluated in dog and human liver microsomes according to standard procedures for their ability to be hydrolysed to the parent acid. The results are given in the table below.



R	Example	Acid production		Buffer pH 7.5 t1/2 h	SGF pH 1.2 t1/2 h
		Dog mic	Human mic		
	9	100%	80%	3	3.5
	10	100%	75%	1	1
	11	100%	65%	3.5	2.5
	12	100%	60%	>4	1.5
	13	100%	50%	3	7
	14	100%	70%	5-7	58
	15	100%	100%	8-9	25
	16	100%	45%	1.5	
OEt	6	10%	<2%		

Acid production - % conversion of test ester to parent acid by dog or liver microsomes after incubation of 1µm test compound for 15 min, determined by measuring the concentration of parent acid produced by HPLC detection of acid (100% = 1µM acid produced). Figures are rounded to nearest 5%.

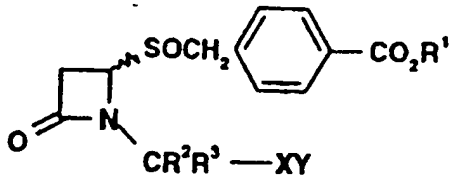
3. Evaluation of stability

Stability was estimated by determining half lives for decomposition test compound in pH 7.5 buffer (50 mM phosphate) and pH 1.2 buffer (USP simulated gastric fluid = NaCl/HCl pH 1.2 + pepsin). Initial concentration = 50 uM and compound monitored by HPLC. Figures rounded to nearest 0.5 h.

Preferred compounds are those exhibiting good conversion of ester to acid in biological systems, while showing good stability in buffers (e.g. examples 9, 11, 12, 15, 16).

Claims

1. A compound of the formula (I):



(I)

in which:

R^1 is hydrogen or a corresponding pharmaceutically acceptable ester or a pharmaceutically acceptable salt thereof;

R^2 and R^3 which may be the same or different is each selected from hydrogen or optionally substituted $C_{(1-6)}$alkyl;

X is a group $X'(CH_2)_m$ in which X' is CO, $CONR^4$, COO, $CONR^4CO$, CONHO or CH_2O in which R^4 is hydrogen or $C_{(1-6)}$alkyl and m is 0 or an integer from 1 to 12; or a $C_{(1-12)}$alkylene chain optionally interupted by X'; and

Y is an optionally substituted aryl group;

having the absolute configuration (4*R*,*SS*).

2. A compound as claimed in claim 1 in which R^2 and R^3 is each hydrogen or R^2 is hydrogen and R^3 is methyl.

3. A compound of formula (I) as claimed in claim 1 or 2 in which X is $CO(CH_2)_m$, $CONH(CH_2)_m$, $COO(CH_2)_m$, $CONHCO(CH_2)_m$, $CONHO(CH_2)_m$, $CH_2O(CH_2)_m$, or $C_{(1-12)}$alkylene.

4. A compound of formula (I) as claimed in any one of claims 1 to 3 in which X is $CONH(CH_2)_m$ or $CH_2O(CH_2)_m$.

5. A compound of formula (I) as claimed in any one of claims 1 to 4 in which X is $CONH(CH_2)_6$.

6. A compound of formula (I) as claimed in any one of claims 1 to 5 in which Y is phenyl, optionally substituted by up to three further substituents

7. A compound of formula (I) as claimed in any one of claims 1 to 6 in which Y is phenyl optionally substituted by halo.

8. A compound of formula (I) as claimed in any one of claims 1 to 7 in which X-Y is $CONH(CH_2)_6Ph(4\text{-}F)/(4\text{-}Cl)$.

9. A compound of formula (I) as claimed in any one of claims 1 to 8 in which the pharmaceutically acceptable ester is a $C_{(1\text{-}6)}$alkyl or $C_{(2\text{-}6)}$alkenyl ester or a pharmaceutically acceptable *in vivo* hydrolysable ester.

10. A compound of formula (I) as claimed in 9 in which R^1 for use in an *in vivo* hydrolysable ester is selected from:

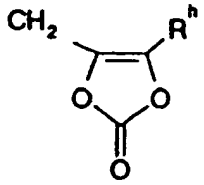
$-CH(R^a)O.CO.R^b$;

$-CH(R^a)O.CO.OR^c$;

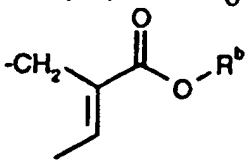
$-CH(R^a)CO.NR^eR^f$

$-R^dNR^eR^f$;

$-CH_2OR^g$;



$-CH(R^a)O.CO.C_6H_4Y^1COCH(R^i)NH_2$; and



in which:

R^a is hydrogen, $(C_1\text{-}6)$alkyl, in particular methyl, $(C_3\text{-}7)$cycloalkyl, or phenyl, each of which may be optionally substituted;

R^b is $(C_1\text{-}6)$alkyl, $(C_1\text{-}6)$alkoxy$(C_1\text{-}6)$alkyl, phenyl, benzyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl, 1-amino$(C_1\text{-}6)$alkyl, or 1-$(C_1\text{-}6$alkyl)amino$(C_1\text{-}6)$alkyl, each of which may be optionally substituted; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^c is $(C_1\text{-}6)$alkyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl;

R^d is $(C_1\text{-}6)$alkylene optionally substituted with a methyl or ethyl group;
R^e and R^f which may be the same or different is each $(C_1\text{-}6)$alkyl; or aryl$(C_1\text{-}4)$ alkyl, optionally substituted with e.g. hydroxy;
R^g is $(C_1\text{-}6)$alkyl;
R^h is hydrogen, $(C_1\text{-}6)$alkyl or phenyl;
R^i is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, $(C_1\text{-}6)$-alkyl, or $(C_1\text{-}6)$alkoxy;
and
Y^1 is oxygen or NH.

11. A compound of formula (I) as claimed in claim 10 in which R^1 is:
(a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl, (1-aminoethyl)carbonyloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl and 4-methoxyphenyl-carbonyloxymethyl;
(b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl;
(c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;
(d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;
(e) lactone groups such as phthalidyl and dimethoxyphthalidyl;
(f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; and
(g) (2-methoxycarbonyl-*E*-but-2-en-yl)methyl.

12. Acompound of formula (I) as claimed in claim 11 in which R^1 is:
(2-methoxycarbonyl-*E*-but-2-en-yl)methyl, isobutyryloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl, 4-methoxyphenyl-carbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxy-carbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl,

N,N-dimethylaminocarbonylmethyl, or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.

13. A compound of formula (I) selected from:
(4*R*, *SS*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide (and pharmaceuticaly acceptable salts thereof, in particular the sodium salt);
(4*R*, *SS*)-N-[6-(4-Fluorophenyl)hex-1-yl]-4-(4-alloxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-(4-Fluorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide;

(4*R*, *SS*)-N-(6-(4-Chlorophenyl)hexyl)-4-(4-ethoxycarbonylbenzylsulphinyl)-2-oxoazetidin-1-ylacetamide;

(-)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2);
(+)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2);
(+)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast. 2);
(-)-1-(2-(6-Fluorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine (diast. 2);

(-)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2);
(+)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-carboxybenzylsulphinyl)-2-oxoazetidine (diast. 2);
(+)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine;
(-)-1-(2-(6-Chlorophenyl)hexyloxy)ethyl-4-(4-allyloxycarbonylbenzylsulphinyl)-2-oxoazetidine;

(α-S, *4*-R, *S*-S)-N-[6-(4-fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide;
(α-S, *4*-R, *S*-S)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide;

(α-R, *4*-R, *S*-R)--N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide;
(α-R, *4*-R, *S*-S)-N-[6-(4-Fluorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl)]-2-oxoazetidin-1-ylpropionamide;

(-)-(α-S, *4*-R, *S*-S)-N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide ((-)B2);
(-)-(α-S, *4*-R, *S*-S)-[6-(4-Chlorophenyl)hexyl]-2-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide;

(+)-(α-R, *4*-S, *S*-R)-N-[6-(4-Chlorophenyl)hexyl]-2-[(4-allyloxycarbonyl)benzylsulphinyl]-2-oxoazetidin-1-ylpropionamide ((+)B2); and
(+)-(α-R, *4*-S, *S*-R)-N-[6-(4-Chlorophenyl)hexyl]-2-(4-carboxybenzylsulphinyl)-2-oxoazetidin-1-ylpropionamide.

14. A compound of formula (I) selected from:
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(cyclohexyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(tert-butyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(1-methylcyclohexyloxycarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(phenylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(4-methoxyphenylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(iso-butyryloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(2-methoxyprop-2-ylcarbonyloxymethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, *SS*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-((5-methyl-2-oxo-1,3-dioxolen-4-yl)methyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;

(4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-((2-methoxycarbonyl-*E*-but-2-en-yl)methyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;
(4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(N-N-dimethylaminocarbonylmethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide; and
(4*R*, S*S*)-N-(6-[4-Fluorophenyl]hex-1-yl)-4-(4-(N-N-di-(2-hydroxyethyl)aminocarbonylmethyloxycarbonyl)benzylsulphinyl)-2-oxoazetidin-1-yl)acetamide;

15. A pharmaceutical composition comprising a compound of formula (I) as defined in any of the preceding claims and a pharmaceutically acceptable carrier.

16. A compound of formula (I) as defined in claim 1 for use in therapy.

17. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating atheroscelrosis.

18. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating diabetes, hypertension, angina pectoris, after ischaemia, reperfusion, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation, inflammatory conditions of the brain such as Alzheimer's Disease, neuropsychiatric disorders such as schizophrenia, and psoriasis.

19. A method of treating a disease state associated with activity of the enzyme Lp-PLA2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme.

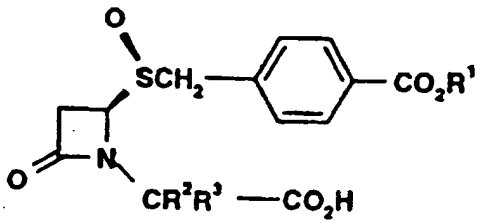
20. A method as claimed in claim 19 in which the disease state is associated with the increased involvement of monocytes, macrophages or lymphocytes.

21. A method as claimed in claim 19 in which the disease state is associated with the formation of lysophosphatidylcholine and oxidised free fatty acids.

22. A method as claimed in claim 19 in which the disease state is associated with lipid peroxidation in conjunction with Lp PLA2 activity.

23. A method as claimed in claim 19 in which the disease state is associated with endothelial dysfunction.

24. A process for preparing a compound of formula (I) as defined in claim 1 and in which X is an amide CONH which comprises treating a compound of formula (II):



(II)

in which R^1 is $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl and R^2 and R^3 are as defined in claim 1, and having the absolute configuration (*4R,SS*);
with an amine of the formula (III):

$$H_2N(CH_2)_nY$$

(III)

under suitable amide forming conditions, for instance in the presence of an activating agent such as N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in a suitable solvent such as dry dimethylformamide; and thereafter, and if necessary,

(a) removing the ester group under suitable de-esterifying conditions to form the acid;

(b) converting the acid to a pharmaceutically acceptable salt; and/or

(c) converting the acid, a suitable salt, the ester or an activated derivative of the acid, to an *in vivo* hydrolysable ester by reaction with a compound of formula (IV):

$$R^1R^4$$

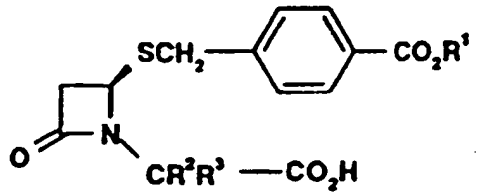
(IV)

in which:

R^4 is a reactive esterifying leaving group; and

R^1 is as hereinbefore defined;
under ester forming conditions.

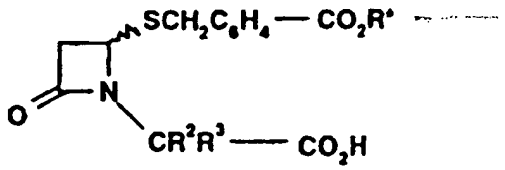
25. A compound of formula (V):



(V)

in which R^1, R^2 and R^3 are as defined in claim 1, and having the absolute configuration (4*R*);
having the absolute configuration (4*R*).

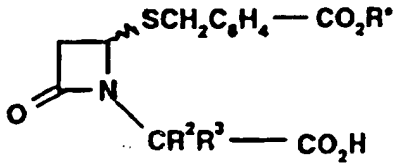
26. A diastereoisomeric salt formed from a compound of formula (VI):



(VI)

in which R* is a carboxy protecting group, for instance $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl and R^2 and R^3 are as defined in claim 1; and
a chiral base.

27. A process for resolving an intermediate compound of formula (VI):



(VI)

in which R* is carboxy protecting group, for instance a $C_{(1-6)}$alkyl or $C_{(2-6)}$alkenyl and R^2 and R^3 are as defined in claim 1;

which process comprises the formation of a diastereoisomeric salt with a chiral base such as (-)-cinchonidine.

28. A process for preparing a compound of formula (I) as defined in claim 1 and in which X is an amide CONH which comprises the process defined in claim 27.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D205/09 A61K31/395 C07D405/12 //(C07D405/12,205:00, 317:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 13636 A (MERCK & CO INC ;DAVIES PHILIP (US); DOHERTY JAMES B (US); FINKE PA) 23 June 1994 see the whole document ---	1-18, 24-28
Y	EP 0 525 973 A (MERCK & CO INC) 3 February 1993 see the whole document ---	1-18, 24-28
Y	WO 94 10142 A (MERCK & CO INC ;DOHERTY JAMES P (US); DORN CONRAD P (US); DURETTE) 11 May 1994 see the whole document ---	1-18, 24-28
Y	EP 0 481 671 A (MERCK & CO INC) 22 April 1992 see the whole document ---	1-18, 24-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 1997	10.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 337 549 A (MERCK & CO INC) 18 October 1989 see the whole document	1-18, 24-28
Y	EP 0 199 630 A (MERCK & CO INC) 29 October 1986 see the whole document	1-18, 24-28
Y	WO 93 02048 A (SCHERING CORP) 4 February 1993 see the whole document	1-18, 24-28
Y	WO 95 00649 A (SMITHKLINE BEECHAM PLC ;MACPHEE COLIN HOUSTON (GB); TEW DAVID GRAH) 5 January 1995 cited in the application see the whole document	1-18, 24-28
Y	WO 95 09921 A (ICOS CORP) 13 April 1995 cited in the application see the whole document	1-18, 24-28
P,X	WO 96 29307 A (JAPAN TOBACCO INC ;TSUTSUMI KAZUHIRO (JP); INABA TAKASHI (JP); TAN) 26 September 1996 see the whole document	1-18, 24-28
P,X	WO 96 19451 A (SMITHKLINE BEECHAM PLC ;HICKEY DEIRDRE MARY BERNADETTE (GB); DHANA) 27 June 1996 cited in the application see the whole document	1-18, 24-28
P,X	WO 96 13484 A (SMITHKLINE BEECHAM PLC ;HICKEY DEIRDRE MARY BERNADETTE (GB); DHANA) 9 May 1996 cited in the application see the whole document	1-18, 24-28
P,X	WO 97 02242 A (SMITHKLINE BEECHAM PLC ;DHANAK DASHYANT (GB); HICKEY DEIRDRE MARY) 23 January 1997 cited in the application see the whole document	1-18, 24-28
E	WO 97 21676 A (SMITHKLINE BEECHAM PLC ;HICKEY DEIRDRE MARY BERNADETTE (GB); DHANA) 19 June 1997 see the whole document	1-18, 24-28

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413636 A	23-06-94	US 5348953 A	20-09-94
		AU 5802894 A	04-07-94
EP 0525973 A	03-02-93	AU 660026 B	08-06-95
		AU 1858292 A	10-09-92
		AU 656591 B	09-02-95
		AU 1858392 A	07-01-93
		CA 2072215 A	26-12-92
		CN 1068815 A	10-02-93
		JP 6329625 A	29-11-94
		JP 8025994 B	13-03-96
		JP 6009550 A	18-01-94
		JP 7084435 B	13-09-95
		NZ 243287 A	27-08-96
		NZ 270150 A	27-08-96
		WO 9300332 A	07-01-93
		US 5348953 A	20-09-94
WO 9410142 A	11-05-94	AU 663806 B	19-10-95
		AU 5028393 A	12-05-94
		CA 2108584 A	28-04-94
		CN 1090272 A	03-08-94
		CZ 9501068 A	13-03-96
		EP 0595557 A	04-05-94
		FI 951992 A	26-04-95
		HR 931309 A	28-02-97
		HU 9500639 A	28-11-95
		HU 72084 A	28-03-96
		JP 6263723 A	20-09-94
		JP 8002868 B	17-01-96
		NO 951593 A	23-06-95
		PL 308545 A	21-08-95
		SI 9300566 A	30-09-94
		SK 53795 A	13-09-95
		ZA 9307949 A	02-09-94
		US 5591737 A	07-01-97
EP 0481671 A	22-04-92	AU 648345 B	21-04-94
		AU 8583391 A	19-12-91
		CA 2052973 A	16-04-92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0481671 A		JP 5132458 A	28-05-93
		US 5229381 A	20-07-93
EP 0337549 A	18-10-89	AT 128704 T	15-10-95
		AU 1858292 A	10-09-92
		AU 3263089 A	12-10-89
		CA 1337990 A	23-01-96
		CN 1037144 A	15-11-89
		DE 68924439 D	09-11-95
		DE 68924439 T	09-05-96
		DK 169329 B	10-10-94
		ES 2079373 T	16-01-96
		JP 2006471 A	10-01-90
		LV 11459 B	20-12-96
		PT 90222 B	29-07-94
		US 5229381 A	20-07-93
EP 0199630 A	29-10-86	US 4680391 A	14-07-87
		CA 1286304 A	16-07-91
		JP 61289074 A	19-12-86
		US 5229381 A	20-07-93
		US 5229510 A	20-07-93
WO 9302048 A	04-02-93	AU 658441 B	13-04-95
		AU 2398092 A	23-02-93
		BG 61118 B	29-11-96
		CA 2114007 A	04-02-93
		CN 1069024 A	17-02-93
		CZ 9400142 A	13-07-94
		EP 0524595 A	27-01-93
		EP 0596015 A	11-05-94
		HU 67341 A	28-03-95
		JP 2525125 B	14-08-96
		JP 6508637 T	29-09-94
		NO 940221 A	21-01-94
		NZ 243669 A	22-12-94
		OA 9878 A	15-09-94
		SK 7994 A	06-07-94
		US 5561227 A	01-10-96
		US 5306817 A	26-04-94

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9500649 A	05-01-95	EP 0658205 A	21-06-95
		JP 8500740 T	30-01-96
WO 9509921 A	13-04-95	CA 2151045 A	13-04-95
		EP 0673426 A	27-09-95
		JP 8504603 T	21-05-96
		US 5641669 A	24-06-97
		US 5532152 A	02-07-96
		US 5605801 A	25-02-97
WO 9629307 A	26-09-96	AU 5014496 A	08-10-96
WO 9619451 A	27-06-96	AU 4389896 A	10-07-96
WO 9613484 A	09-05-96	AU 3869895 A	23-05-96
		ZA 9509100 A	20-06-96
WO 9702242 A	23-01-97	AU 6305096 A	05-02-97
WO 9721676 A	19-06-97	NONE	